RPB

# EYE RESEARCH SEMINAR

A Compilation of Papers Presented at the First
NATIONAL SCIENCE WRITERS SEMINAR IN
OPHTHALMOLOGY
Held at Washington, D.C., Nov. 6-9, 1965

*Under the sponsorship of*

RESEARCH TO PREVENT BLINDNESS, INC.
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# RESEARCH TO PREVENT BLINDNESS, INC.

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Dear Doctor:

The papers presented here cover a broad range of interests in the field of ophthalmology. They were prepared by men whose names will be recognized as distinguished representatives of the areas they have chosen to discuss. These were the participating panelists in the National Science Writers Seminar in Ophthalmology conducted by Research to Prevent Blindness, Inc. (RPB) in November, 1965, the first ever held in this field. The papers provide a splendid overview of problems and progress in modern eye research.

The Seminar marked a very large step in spotlighting the nature of visual loss and awakening popular interest in the preservation of sight. Public misunderstanding and lack of knowledge of the visual processes have been major factors in neglect of the eyes. In bringing together for the first time the nation's foremost ophthalmic scientists and its top science writers, RPB created a springboard for authentic news about vision which reached millions of Americans through news media in every part of the country.

The participating scientists were asked to write their papers in such a manner that they might easily be translated to the public. The written texts were delivered to the writers in advance of the panel meetings so that each session might be devoted to full discussion of their content. The material should provide valuable information for the practicing ophthalmologist and others with professional interest in the enigma of sight. In addition, RPB hopes they will become a welcome resource which may be drawn upon at will by those who have occasion to address interested lay groups.

It is RPB's purpose to open up channels of communication in a field of medical science that has suffered much for want of voice. There are always gaps in communication between scientists, between scientists and clinicians, and between physicians and the general public. In ophthalmology the problem is especially serious, and as a result the natural growth of this particular science in an era of scientific explosion has been seriously impeded.

The Trustees of Research to Prevent Blindness, Inc. are confident that you whose lives are dedicated to the prevention of blindness will find these presentations useful in opening more eyes to the enormous potential of eye research in the eradication of blinding diseases.

Robert E. McCormick
President
Research to Prevent Blindness, Inc.

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# EYE RESEARCH—THE KEY TO BLINDNESS PREVENTION

**Jules C. Stein, M.D.**

*Chairman, Research to Prevent Blindness, Inc., New York, New York*

Dr. Stein is chairman of Research to Prevent Blindness, Inc., a national voluntary foundation established to meet the need for aggressive action in support of research to find and eradicate the causes of blinding diseases. A Fellow of the American Board of Ophthalmology, he was a practicing ophthalmologist before embarking on a business career that finds him today a legend in the entertainment world and chairman of MCA, Inc. Dr. Stein received his M.D. degree from Rush Medical College in 1921 and later studied at the University of Vienna under the eminent Dr. Ernst Fuchs. In 1964 he was elected to honorary membership in the Association for Research in Ophthalmology for "infusing life and energy into the total field of ophthalmic research". A new eye research center at the University of California, Los Angeles is to be named in his honor.

It is gratifying to me and, I am sure, to all others concerned about eye diseases that news organizations have assigned their writers to this Seminar. The eminent men of science and medicine who will address you during five sessions will make it worth your while. They will describe for you a truly horrifying situation in which this nation, heedlessly and needlessly, is drifting into a growing sea of blindness. And they will tell you about some of the remarkable discoveries which recently have been made in their pursuit of the causes, the prevention and the cures of various serious eye diseases.

Blindness—total and partial—is not just another disease with which to worry a population already harrassed by the multitudinous problems of health and national and world affairs.

Visual disorders constitute the nation's leading cause of disability. Loss of sight must be recognized as a world-wide plague. Moreover, the great and growing number of blind persons is the result of their excommunication from the benefits of the current science explosion.

A great pity is that so much blindness is unnecesssary; it is preventable. And some of it, even though it has begun its insidious course, is curable or controllable under proper medical management.

A greater pity still is that there is little prospect at present of alleviating this situation. People still ignore—or are unaware of—the fateful early signs of a developing eye disease (more than one million middle-aged Americans have glaucoma and don't know it). Too many people are convinced that most blindness is caused by accidents and injuries—a fact brought out emphatically in a recent Gallup poll. Actually only five percent of all blindness in the United States is so caused. The overwhelming causative factors are diseases about which science knows almost nothing, and which the individual can do nothing to prevent. He can only be alert, and try to deal with the disease after it happens.

Unfortunately, even here we find public lack of knowledge entering into the picture. Only 16 percent of the people in the nation recognize that the ophthalmologist is the one specialist, the medical doctor, who is medically qualified to treat the eye—the man to be seen for complete eye examination. Yet the number of ophthalmologists is small – much too small to meet increasing demands for their clinical services. Vastly smaller is the number of ophthalmologists engaged in research, ridiculously small when we realize the extent of man's visual problems.

Perhaps the most discouraging aspect of the whole picture is the fact that only a tiny and very inadequate sliver of the nation's research dollar is being given over to the enormous problems of eye research. Yet the cause of blindness is unknown in eight of every ten cases. The finest ophthalmologists in the world are helpless against a great majority of eye diseases; they will remain impotent to help countless millions of victims until we increase the capacity of ophthalmic scientists to carry on productive research. There is little evidence of a disposition on the part of government or voluntary granting agencies to support the vast amount of basic and clinical research needed to resolve this problem. For some unfathomable reason, we prefer to practice the foolish economy of laying out more than one billion dollars each year to care for the blind rather than spend a small fraction of that sum to finance research leading to the prevention and cure of blinding diseases.

It is time we stopped being content to pat ourselves on the back for all the good things we do for people after they are blind, and start moving vigorously into research.

We have a good idea of both the dimensions of the problem of eye disease and of the public's interest in this situation. Early this year RPB concluded a nationwide study into the present status of ophthalmic research and the expansion needed to bring this research into line with similar studies in other areas of medical science. One of the major findings of that study was the absence of adequate communications between ophthalmic scientists and the public. This Seminar reflects RPB's intent to correct that deficiency. Within the last three weeks the Gallup Organization, Inc., delivered to RPB the results of its poll on the public's knowledge of eye problems and its attitudes toward research, which I have already mentioned. Both reports have been made available to writers.

To me, the most striking results of the Gallup poll lay in 1) the public's ignorance of the fundamentals of eye disease, 2) the widespread fear of blindness, and 3) the desire for increased research into conditions leading to blindness. The fact that glasses were said to be worn in three out of every four families and that serious eye disease was reported in one of every ten families makes vision troubles a very personal matter to a large segment of the population.

Research offers us scores of opportunities to avert the tragedy of blindness.

In clinical research we might ferret out and save many thousands with presumably cured, but actually latent, syphilis which may destroy their sight and their minds; we could restore sight with plastic and transplanted materials; withhold common drugs from those who may be blinded by them; recognize and compensate for the stresses of flight, cold, underwater exposure and other conditions which impair vision; detect inherited tendencies toward glaucoma, eye cancers and other genetic faults; diagnose reparable eye conditions in infants, and recognize eye disease as the cause of poor scholarship. Despite considerable progress in surgery and other treatments, there remain innumerable avenues of approach to even more effective therapies for many eye conditions.

Beyond this, there is a great need for basic research into the functions of the healthy and diseased visual systems, for improved communications between those who bear the responsibility of bringing modern medicine to patients, for the education and training of hundreds of eye doctors and researchers, and for the creation of the buildings and facilities they will need.

In summary: Despite the alarming increase in incidence of eye diseases, despite the public's expressed desire that our burgeoning ranks of researchers turn more of their attention to this situation, and despite the fact that 80 percent of all blindness results from diseases whose causes are unknown to science, very little is being done about it. Of the billions of dollars now being spent on disease-centered research, on space exploration and other important scientific objectives, only about ten millions are invested each year in the attempt to find causes, preventives and controls for diseases that destroy sight. This is approximately the cost of the one Agena rocket that was lost in the Atlantic Ocean two weeks ago.

This disregard for the nation's vision is pointed up by the fact that almost 90 million Americans have some kind of eye trouble—and in 3,500,000 the trouble is serious.

With proper diagnosis and medical attention, it is possible to save many of these people from losing vision. But, when you consider that one-tenth of all patients seen at our hospitals are eye patients, the true scope of the problem becomes apparent.

It is time we recognized that care and treatment and surgery for those threatened by blindness are merely substitutes for the scientific knowledge that will wipe out these blinding diseases at their source. Federal and private granting agencies will have to recognize the facts of life and act now if we are to stop this nation from losing its sight.

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***The following material is excerpted from the Public Opinion Survey conducted by The Gallup Organization, Inc. for Research to Prevent Blindness, Inc. and to which reference is made in the text above.***

### What Disease or Affliction is Most Feared?

When shown a list of eight afflictions, approximately six out of every ten (62%) respondents felt that Cancer was "the worst thing that can happen to you." Blindness was the next most feared affliction, with nearly one out of every five respondents (18%) naming it as such. Heart disease was named by 9 per cent, while the five other afflictions were each named by 3 per cent or less.

When these findings are analyzed by age and education there is very little variation among the groups with respect to cancer. However, there seems to be a slight tendency for the better educated groups and for middle aged and older people to fear blindness more than their less educated and younger counterparts, as is shown in the table below:

| | Blindness Is "The worst thing that can happen to you" |
|---|---|
| | % |
| National | 18 |
| Education | |
| College | 21 |
| High School | 18 |
| Grammar School | 15 |
| Age | |
| 21-34 years | 14 |
| 35-49 years | 20 |
| 50 years or older | 19 |

### How Well Informed is the Public About Diseases of the Eye?

Very few people are informed about most of the diseases of the eye. Less than two out of every one hundred people were able to identify Uveitis, Amblyopia, and Senile Macular Degeneration as eye diseases. Similarly only one out of every ten were able to identify Trachoma, and three out of ten were able to identify Myopia as an eye disease.

There are substantially more people who hold some information about Glaucoma and Retinal Detachment, with five out of ten and six out of ten respondents respectively saying they are eye diseases.

It is only with respect to Cataracts that there is a high incidence of informed people, with approximately eight out of every ten respondents knowing it is an eye disease. This knowledge level is comparable with that held for Arthritis and Polio.

Many people answered in general terms, referred to the effect of the disease, or gave answers that were vague or incorrect in details. When only those replies that are medically specific and correct are considered, levels of knowledge are drastically lower:

| | Identified Each Correctly | |
|---|---|---|
| | In Part or Completely | Medically Specific |
| | % | % |
| Polio | 89 | 36 |
| Arthritis | 89 | 25 |
| CATARACTS | 83 | 2 |
| GLAUCOMA | 49 | 2 |
| RETINAL DETACHMENT | 43 | 12 |
| Multiple Sclerosis | 42 | 4 |
| MYOPIA | 23 | 8 |
| TRACHOMA | 9 | * |
| Cystic Fibrosis | 6 | 1 |
| AMBLYOPIA | 2 | * |
| UVEITIS | 1 | * |
| SENILE MACULAR DEGENERATION | * | – |

*Less than one per cent.

### Comparison of the Public's Knowledge of Eye Specialists

Despite the fact that somewhat more people correctly identified ophthalmologist than optometrist, the latter word is identified with the eyes by four times as many people as the former. Many people identify optometrists as "eye doctors", in fact more than the proportion who identify them correctly. In contrast, most people who know that ophthalmologists are concerned with the eye can identify them correctly. There is also considerable confusion with respect to oculists and opticians:

| | Ophthalmologist | Oculist | Optometrist | Optician |
|---|---|---|---|---|
| | % | % | % | % |
| Total Who Identified Each as Concerned With The Eye | 21 | 46 | 80 | 70 |
| Eye Doctor | 16 | 20 | 36 | 20 |
| Eye specialist (non-specific) | 0 | 0 | 4 | 17 |
| Prescribes eye glasses | 0 | 0 | 13 | 0 |
| Makes lenses, sells glasses | * | 7 | 3 | 26 |
| Examines eyes (non-specific) | 5 | 19 | 24 | 7 |

| | IDENTIFIED EACH SPECIALIST CORRECTLY | | | |
|---|---|---|---|---|
| | | Education | | |
| | National | College | High School | Grammar |
| | % | % | % | % |
| Pediatrician | 73 | 95 | 83 | 42 |
| Neurologist | 43 | 75 | 48 | 16 |
| Chiropractor | 43 | 57 | 42 | 36 |
| OPTICIAN | 26 | 44 | 26 | 15 |
| OCULIST | 20 | 33 | 23 | 8 |
| Otolaryngologist | 17 | 43 | 16 | 4 |
| OPHTHALMOLOGIST | 16 | 36 | 16 | 5 |
| OPTOMETRIST | 13 | 31 | 11 | 5 |

### How Many Families Have One or More Members Wearing Glasses?

About three out of every four families (76%) in the U.S. have one or more members wearing eye glasses. This proportion is slightly higher for higher status people, (college educated and professional and business people). It is also somewhat higher in the non-labor force, that is, primarily in older families where the head of the household is retired. This is summarized in the table which follows.

| | Have one or more family members wearing eye glasses |
|---|---|
| | % |
| National | 76 |
| Education | |
| College | 84 |
| High School | 73 |
| Grammar School | 76 |
| Occupation of Head of Household | |
| Professional & Business | 86 |
| Clerical and Sales | 76 |
| Farmer | 81 |
| Manual Worker | 66 |
| Non-Labor Force | 87 |

The projected number of people in the U.S. who wear glasses is approximately 75,000,000.

Roughly half of the civilian adult population (51%) report they have had an eye examination within the past two years and over ninety per cent had their eyes examined at some point.

| | National |
|---|---|
| Had Eyes Examined Last | % |
| Within the past two years | 51 |
| Two years ago or more | 39 |
| Don't remember when | 2 |
| Never | 8 |
| | 100 |

### How Many Families Have One or More Members With Serious Eye Problems?

Almost one out of every ten families (7%) report they have a member with a serious eye problem. Again this is more prevalent in the families where the head of household is not in the labor force and also in the lower income groups.

| | Has one or more family members with serious eye problem |
|---|---|
| | % |
| National | 7 |
| Occupation of Head of Household | |
| Professional & Business | 5 |
| Clerical & Sales | 5 |
| Farmer | 3 |
| Manual Worker | 5 |
| Non-Labor Force | 16 |
| Annual Family Income | |
| $10,000 and over | 7 |
| $7,000 - $9,999 | 4 |
| $5,000 - $6,999 | 6 |
| $3,000 - $4,999 | 5 |
| Under $3,000 | 11 |

The projected number of people in the U.S. reported to have serious eye problems is approximately 3,500,000.

### How Well Informed Is the Public About the Incidence and Causes of Blindness in the U. S.?

When asked to estimate the number in the U.S. who are blind, the median response of the general public was one million. There is virtually no difference in the estimates made by persons at the different levels of education.

When given a list of five types of causes of blindness, thirty-nine per cent of the public selected eye diseases like cataract and glaucoma as the most frequent cause of blindness. Another twenty-three per cent selected injuries and accidents as the most frequent cause of blindness.

| | National |
|---|---|
| Most Frequent Cause of Blindness | % |
| Eye diseases like cataract and glaucoma | 39 |
| Injuries and accidents | 23 |
| General diseases like diabetes, diseases of blood vessels, etc. | 13 |
| Infections and infectious diseases | 10 |
| Heredity | 6 |
| Other | * |
| Don't know | 9 |
| TOTAL | 100 |

*Less than one per cent.

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# THE MECHANICS OF VISION
## (How We See)

George K. Smelser, Ph.D.
*Columbia University, New York, N.Y.*

Dr. Smelser is professor of anatomy at Columbia University. He holds the Research Career Professorship Award. The author of the classic text, "Structure of the Eye," Dr. Smelser holds membership in the American Association of Anatomists, the American Society of Zoologists, the Society of Experimental Biology and Medicine, the Harvey Society and the Association for Research in Ophthalmology.

The purpose of my remarks is to explain "how we see" in as direct and simple a manner as possible, trying to give a concept of the structures of the eye and their functions. I would like to do this by first outlining how we believe this complicated yet beautifully integrated organ came into being. A fundamental characteristic of living things is the ability to sense and react to their physical environment. Among the stimuli which animals sense, such as heat, cold, pressure, or touch, and sound, is light. Primitive organisms sense light by means of more or less specialized areas of the single cell. In multi-celled animals, certain cells become specialized to sense light and are often found grouped together and associated with nerves, which relay the information they obtain to a central neural system. In order that light should reach the light perceiving cells, these are often on or very near the surface of the body and, therefore, exposed to possible injury. One should note that this system is limited to distinguishing light and dark; however it is a primitive "eye."

The eye of the vertebrate is far more complex, since it is designed not only to sense light and dark, but also to distinguish form, which means that an image must be produced on the light sensitive cells. An image is made of a nearly infinite number of light and dark points, which must be interpreted by a "computer" in the neural system so that the brain appreciates contours, edges, or shapes. Part of the work by means of which data are integrated is done by the brain itself, but a great deal of interpretation occurs in the retina, the layer of cells inside the eye which is made up of light sensitive structures and their immediate neural connections. The retina is, therefore, the essential element of the eye. This arrangement is not astonishing because the retina is, in vertebrates, a part of the brain and forms as such in the embryo. It is not just a peripheral collection of highly specialized nerve cells. The function of image perception added to light perception requires complicated accessory structures to form the image and to nourish, service, and protect the retina. As in man-made gadgets, increasing complexity and sophistication multiply the number of potential failures of the mechanism.

Clinical ophthalmology deals, in my opinion, more with the problems of the accessory structures than with those of the light perceiving tissue itself. That is not to say that the mechanism of light perception is faultless, but that the relatively rare difficulties which affect it are so subtle in nature that, to date, laboratory investigators and clinicians alike have very little to offer. I am excepting the problems caused by gross dislocation, or detachment of the retina from underlying structures.

With this preamble, let me offer a resumé of eye anatomy intended to set the stage for the more pertinent reports to follow. The eye is a nearly spherical structure about one inch in diameter. It is constructed of several layers, distinct in structure and function. The outer layer is, in the rear or posterior portion, opaque, white and tough but not rigid. It is most appropriately designated the sclera, and in function it is protective. In the anterior part this layer is still tough, but instead of opaque and white, it is very transparent and is called the cornea. Light penetrates it readily; it is the most transparent colorless tissue of the body. Any deterioration in the transparency of the cornea renders the light perceiving structures, deep within the eye, valueless in proportion to the loss of transparency. Also of prime importance to the cornea is the curvature of its surface. If an image is to be formed on the retina, a lens system must be incorporated in the eye. A major part of this function is mediated at the front surface of the cornea, which must be optically smooth and possess a curvature that is regular, as in any good optical system. If the radius of the curvature differs in the horizontal and vertical meridians, an astigmatism exists. Occasionally, the radius of curvature is irregular, as in conical cornea, or the surface is wrinkled, which destroys or impairs the image forming function.

One way in which surgeons have sought to correct difficulties caused by irregularly curved or opaque corneas is to transplant normal corneas in place of the valueless ones. In suitable cases, this procedure has produced very satisfactory results, a fact which has astonished many surgeons, since experience generally tells us that one may not transplant tissue from one individual to another without difficulty. This is because the body recognizes the transplanted tissue as not being its own and attacks it by immunological processes as it does any other foreign material. This led to the supposition that perhaps the cells of the cornea do not survive transplantation, and the graft was simply made over by the host into its own tissue. Recently, experiments utilizing reliable methods for identifying cells have shown that this idea was not correct. A clear corneal transplant may very well contain living cells of the donor tissue. This has an interest aside from the obvious scientific one, for many, many persons ask: Will my cornea continue to live after I have given it to another? It will. It could be imagined that at least this part of our body could, by successive transplantation, achieve a kind of immortality, though not a very satisfactory one by most standards.

Inside the outer corneo-sclerotic layer lies the uveal layer, which is primarily nutrient in function. This layer may be divided into an anterior or front part, which includes the iris and ciliary body, and a back part or the choroid. All of it is a loose tissue made of blood vessels held together by delicate connective tissue fibrils in which are lodged many cells characteristic of loose vascular connective tissue elsewhere in the body. Among these cells are melanin-bearing pigment cells, of which one often hears because of the development of malignant tumors of these cells (melanomas) in the eye. Later, you will also hear of inflammation (uveitis) of this part of the eye, which is a major cause of blindness. The retina lies directly on the choroid pressing the light perceiving elements close to the capillaries of the choroid from which they derive their nutrition. This includes not only the metabolites, which are necessary for the maintenance of all cells, but also the materials essential for the specific process of vision, the precursors of visual pigments such as rhodopsin.

The light perceiving mechanism is so exquisitely sensitive that it is easy to overload it with too much light. A light regulating mechanism provides a movable curtain, the iris, in the anterior part of the eye which, by its contraction or relaxation, admits more or less light. This movement is accomplished by delicate muscles within it, which are controlled by the involuntary nervous system, receiving its stimuli via a feedback mechanism from the retina. The movement enlarges and contracts the round opening in the iris, the pupil. Behind it lies the lens, the second of the devices (after the cornea) by means of which an image is formed on the retina, making possible perception of shapes and high precision (acuity) of vision. The radius of the curvature of the lens is changeable, and focusing on near and far objects is, therefore, possible. This is achieved by distorting the plastic substance of the lens by an elastic membrane which surrounds it. Tension on this membrane varies from moment to moment by movement of the ciliary body, which contains a system of muscles. The ciliary body transmits the tensions created by its movement to the lens via numerous fine fibrils. The lens may give us trouble by becoming opaque (a cataract). This does not astonish biologists, because it is made of a flat sheet of cells, converted to a vesicle with the free surface inward, just as a flat sheet of leather can be converted to an old-fashioned tobacco pouch. This bag, or lens, is filled with cells formed from the flat sheet from which they cannot escape or be sloughed off, as they would be on the surface of the body. Instead, they are packed more and more densely and in an exquisitely orderly fashion. As the bag's contents become more and more compacted, they become less and less malleable, less able to change shape and, therefore, to focus. When this occurs, the lens is less useful in adjusting to near and far vision and it is said that we are presbyopic, which happens to most of us in the mid-forties. A further extension of this process leads to opacity. One may consider, therefore, a lens opacity to be the normal destiny of a lens, if one should live long enough. Surgical removal of cataracts is a regularly and skillfully performed feat, which relieves us of an opaque lens, but which does not return our ability to focus on near and far objects.

One may ask by what means nature is able to create such a near-spherical structure with such a perfectly constructed lens-like front surface as is the eye. The eye grows by a process analagous to that of a balloon when it is inflated. If the wall of the balloon is even in thickness and elasticity, a sphere results. In the embryo the vitreous humor, which occupies the major portion of the interior of the eye, behind the lens, grows and distends the coats of the eye into its near-spherical form. In the adult, the vitreous humor acts, in part, to maintain these layers, particularly the retina, in place and in contact with each other. The adult eye is turgid, due to the pressure within it, which is created by a pump-like mechanism producing a constant influx of fluid, the aqueous humor, which drains out of the eye at an equivalent steady rate, thus maintaining a nearly constant intra-ocular pressure. A balance is obviously necessary between input and drainage of this fluid which is kept by a "feedback" mechanism. Although one can be sure that such a mechanism exists, neither the method of sensing the pressure nor that of adjusting the input or output channels is known. Such a delicately balanced mechanism is obviously vulnerable to malfunction. When the pressure rises, almost always resulting from imperfections of the outflow mechanism, the disease glaucoma results. Many surgical and medical techniques have been developed to deal with this condition without, as yet, a clear understanding of either the normal or pathological processes involved.

Now at the close of this discussion, the retina, which is the site of the essential function of the eye and to which all of the other structures we have discussed are really accessory, deserves some comment. The light perceiving cells are the rods and the cones, so named many years ago because of the shape of their outer portion, the "business end" of the cell. These shapes have no real significance and are merely descriptive. The rods are more sensitive than the cones and mediate vision at low light intensity. The cones mediate color vision. The fine structure of both cells as seen with the electron microscope is very similar, but they differ in the nature of the light sensitive pigment which they contain. The latter is a complex of carotenoid pigment and a protein, opsin. The carotenoid is a molecule which exists in different shapes, bent, and straight. The opsin molecule has an indentation on its surface which will just hold the carotenoid when it is bent. Such an arrangement is unstable in light, so that when light strikes it the carotenoid becomes straight and falls out of its niche. Bending the carotenoid occurs elsewhere and requires energy; when it straightens and separates from the opsin under the influence of light energy is released, therefore, light triggers the initial response which in itself requires no energy. It is analagous to releasing an arrow from the bow which requires no energy, energy having been expended in bending the bow. The straightening and release of the carotenoid provides energy which changes the polarization of the membranes of this part of the photoreceptors (rod or cone), and thus the signal of this event is thought to be conveyed to the more proximal part of the cell. From this point the effect of the light stimulus is relayed through the retina and to the brain by the usual neural mechanisms. The lamelles of which this part of each photoreceptor is composed consist of such systematically arranged opsin-carotenoid molecules that they have, in fact, a near crystalline structure. The lamelles appear to be fixed in form and permanent, yet it has been shown by the use of radioactive isotopes that they are continuously being degraded and reformed. New lamelles are fabricated at the base of this part of the cell and as they age, which requires some days, they move outward toward the pigment epithelium, where by means unknown, they are destroyed and their component parts removed. This concept of continuous renewal was not even dreamed of a few years ago.

The rods and cones are of several types, depending on the type of carotenoid which they contain. Recently, this has been shown by a series of fantastically delicate experiments. Individual rods and cones were isolated, and a beam of light only microns in diameter was passed through them and their absorption spectrum measured electronically. By this means, it could be shown that cones fall into three classes with respect to their major light absorption peak. Thus the hypothesis built during the past 100 years through psychobiological experiments was substantiated. To my mind, this is analagous to the final discovery of a celestial body whose existence could only be conjectured indirectly from the orbital pattern of other planets.

The signals initiated in the innumerable rods and cones, as described, are integrated into a complex message and conveyed to the brain via the optic nerve. The retina is, therefore, a computer. The output of many rods and cones is fed into the next neuron of the series in the retina, the bipolar cell. Nerve fibers also run between nearby photoreceptors and between bipolar cells, modifying in turn their neural output. When one realizes that the signal from each photoreceptor is not conveyed directly via a single channel to the brain, but that the information which is collected from a nearly infinite number of photoreceptors is molded into a mental concept of that which is seen, a realization of the complexity of this integrating process begins. To unravel such a mechanism, morphologists literally dedicate their efforts (as was evident from the papers presented at the International Congress of Anatomy at Wiesbaden this summer) to working-out the wiring diagram of the retina. Electro-physiologists, in turn, are probing the retina with micron-sized electrodes, testing these circuits.

"How we see" is an almost infinitely complicated process. It begins with the passage of a beam of light reflected from our environment through the cornea, which is unique with respect to its transparency and the excellence of its anterior lens-like surface. The light is then regulated by a movable diaphragm, the iris, which automatically adjusts the amount which falls on the retina acting in response to a neural "feedback" mechanism. The rays of light are then brought to a final focus on the retina by an adjustable lens, whose colorlessness and transparency is similar to that of the cornea. The rays of light having been brought to focus on the light sensitive layers of the retina initiate the impulse very much, we believe, as has been described. The signals from the many rods and cones are brought together by a computer-like arrangement of neurons, some in the retina and others in the brain, so that a concept is formed of the environment. This mechanism is sustained nutritionally by the delicate vascular choroid, which lies exterior to the retina.

The eye provides investigators with a wealth of opportunities to study the most basic problems of biology. In many instances these are of importance, not only in the eye, but generally. For example, biologists have been concerned with whether nerves wear out. Generally it is believed that neurons are not replaced, but that is not to say that they do not undergo constant reconstruction and repair. Studies were made on peripheral nerves by labeling the axons with radioactive isotopes but the data obtained were difficult to interpret because the nerve fibers were surrounded by many other cells, which may also have been labeled with the isotope. The eye provided the place where this problem could be resolved. The isotopes were injected into the vitreous humor, where they diffused readily into the ganglion cells and became incorporated in the axon substance next to the ganglion body, but not in cells elsewhere in the body. From this point, the labeled axon substance moved peripherally, i.e. out of the eye through the optic nerve to its final destination in the brain. Identification of the renewed axon material in the optic nerve proved beyond doubt that nerves are continuously renewed, a finding which could not have been accomplished excepting in the eye.

# EXPERIMENTAL RETINAL DISEASE AND BLINDNESS

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It is through our senses that we communicate with the outside world. Without them we would be isolated, from one another and from our environment. In man, vision is by far the most important of the senses; some 38 percent of all sensory input to the brain is mediated through the visual system. Thus, blindness is devastating for any individual; and thorough understanding of the visual process is important, not only for the cure of diseased eyes but also to anticipate and prevent eye disease.

In our laboratory one of the approaches to furthering our understanding of the visual process has been to study the response of the retina when it is subject to severe stress. To this end, we have mapped out the electrophysiological, biochemical, and anatomical changes occurring in the retinas of rats becoming blind because of either vitamin A deficiency or an inherited disease similar to retinitis pigmentosa in man. At the present time we are studying in a similar way the effects of continuous light on the retinas of rats.

Vitamin A is all-important to the visual process because it is a direct precursor of the visual pigments, the light-sensing molecules of the eye. The visual pigment molecule consists of slightly oxidized derivative of vitamin A, vitamin A aldehyde, joined to a large protein called opsin. In vitamin A deficiency the eye no longer synthesizes normal quantities of visual pigment, and loss of visual sensitivity eventually results. This condition is called night blindness because it is most noticeable when the light is dim, such as occurs at night; but the loss of sensitivity also is present during the day. With prolonged vitamin A deficiency the visual threshold of an animal or man can rise over 10,000 times.

The visual pigment molecules are packed in the elongated distal portion (outer segment) of the visual cell in a very high concentration. Some 15-30 percent of the dry weight of the outer segment of visual cells may be visual pigment protein, opsin, and disturbance of the opsin molecule results in structural deterioration of the visual cell. In chronic vitamin A deficiency the opsin levels in the eye decline, and structural deterioration of the visual cell occurs. Initially this results in loss of just the outer segment of the visual cell, but eventually the entire cell may degenerate. The other retinal cells are unaffected by vitamin A deficiency, and the retina appears normal except for the lack of visual cells.

If vitamin A is restored to vitamin A deficient rats, recovery of both visual sensitivity and structure can occur if the degeneration of the visual cell has not progressed too far. Visual cells, like all other neural cells, do not regenerate; and once a visual cell is lost it can never be replaced. With just partial degeneration, however, vitamin A therapy will induce regeneration and the entire outer segment of the visual cell may be rebuilt. This last finding is of paramount importance because it seems likely that one might induce recovery in other blinding conditions if proper therapy can be found, even though the photosensitive outer segments of the visual cell have entirely degenerated.

Besides nutritional night-blindness, there are known several inherited conditions whose primary symptom is also night blindness. Retinitis pigmentosa is one such disease in man. These inherited night blindnesses are also known to occur in animal populations and several of the mice colonies used for medical research have been shown to suffer from this affliction. In the inherited blindnesses, the visual cells are selectively destroyed as in nutritional night blindness; and this, along with the similarity of symptoms of night blindness in the two conditions, has led some workers to suggest that these two disease processes are linked. For example, it has been supposed that in the inherited blindness there might be a metabolic defect involving vitamin A or visual pigments, and that this is the cause of the inherited lesion.

To test this hypothesis, we have studied rats with the inherited retinal disease. These animals begin to become night blind at about 18 days of age, and are entirely blind by 60 days. To our surprise, though, biochemical measurements show that in the early stages of the night blindness (18-30 days) the visual pigment level in the diseased eye is greatly *increased* as compared with a normal eye. Thus it is clear that the loss of visual sensitivity in the inherited blindness in the rat is not linked to loss of visual pigment, as in vitamin A deficiency, and that some other cause for the disease must be sought.

The elevated visual pigment levels in the eyes of rats with the inherited retinal dystrophy do eventually decline as the visual cells degenerate, but this loss of pigment and visual cell degeneration can be slowed if the animals are maintained under very dim lighting conditions. It has been possible to prolong vision in such animals until they are 120 days of age, or for twice the length of time they ordinarily perceive light with this disease. This finding is most intriguing, and we now wonder whether in similar human diseases the use of dim light might also protect the eye. We hope to test this idea in the near future by encouraging certain retinitis pigmentosa sufferers to wear dark glasses as much as possible.

Finally, the protective effects of dim light in inherited night blindness raises the question of the effect of prolonged bright light on the normal eye. Mr. Robert Mittenthal and I are currently studying this question and have found, again to our great surprise, that just a few days of continuous light exposure will do permanent damage to the retinas of albino rats; and a week of continuous light may entirely blind an animal. Histological examination of the retinas of these animals shows again that the visual cells are selectively destroyed, and the retinas resemble to a striking degree the final stages of both vitamin A deficiency and inherited retinal blindness.

In all of these studies, it is clear that the primary lesion occurs in the visual cell; the rest of the retina appears quite intact. Thus, the visual cell appears particularly susceptible to insult; and recognition of this fact provides, I think, the guidelines for our future thinking and study on retinal disease and blindness.

# OCULAR PHARMACOLOGY

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Voltaire defined a physician as "a man who pours drugs about which he knows little into patients about whom he knows less." This may no longer be true. From earliest accounts of ocular therapeutics, dating back to three to four thousand years before the Christian era until the present, considerable changes have taken place that have provided us with vastly increased knowledge of drugs. Over the years, therapeutists relied essentially on the more rational use of drugs that were already on hand, which had been discovered empirically. This changed in the fourteenth century with the studies of Ehrlich, who attempted to find specific compounds to attack specific diseases. At the present time, we are in an era in which a particular disease is studied biochemically, genetically, at the enzymatic and electromicroscopic level, so that the fundamental defect can be spotted and an appropriate agent synthesized to counteract the offending factor. Synthetic drugs are evolving that include, among others, hormones, antibiotics, antiviral, antifungal, anticancer, antihypertensive, and anti-inflammatory agents. These are deliberately designed to inhibit or stimulate a particular step in the metabolism of the tissue cell or invading organism.

In the plethora of new agents, attempts have to be made to evaluate each one in the therapeutic armamentarium scale. Is it more effective than previously employed therapy? If not more effective, is it less dangerous? Is it less expensive?

Ophthalmology has shared in these recent changes. The eye has always afforded a wonderful laboratory in which to determine and evaluate the action of drugs. Local anesthetics were first employed in the eye for surgery. Koller, an ophthalmologist, whose last post was at The Mount Sinai Hospital in New York City, introduced cocaine for this purpose in 1884. The significance of this event was immediately recognized as revolutionary in ophthalmology, and a little later, the drug was introduced into general surgery.

Drugs that work on the autonomic nervous system, such as atropine, eserine, and adrenalin, were understood pharmacologically after studies involving the ocular structures. In this manner, a number of agents have been shown to possess additional useful properties. Cortisone was found to work locally when instilled directly into an eye. One of the advantages of ocular therapeutics is that many eye diseases can be treated simply by instilling the medicament into the eye, avoiding the oral, intramuscular, or intravenous routes of administration. More recently, the systemically toxic drug IDU was found to be tolerated in the eye when applied locally. This has merit for the management of some forms of herpes simplex keratitis, a potentially blinding disease.

The eye has proven to be a valuable structure to detect undesirable side action of many drugs. Considerable concern over the untoward effects of drugs used in therapy has evoked large and small commentaries, analyses, symposia, panel discussions, and compilations of indictments for the undesirable results of the use of drugs.

The nature of these effects varies. They are often called the side effects of drugs, the toxic effects, and the adverse effects. There are other terms such as allergic reactions, intolerance, idiosyncracy, and drug-induced diseases, or diseases of medical progress, or iatrogenic disorders.

It is important to understand these terms. A *side effect* is a pharmacologic effect other than one sought for in the particular use of the drug. It might be adverse, or non-therapeutic, or even unpleasant, but not fatal. An *adverse effect* could include a side effect but also includes the non-pharmacologic consequences of drug use—the cosmetic effect of the enlarged black pupil after the use of atropine, the population explosion in India resulting from effective antimicrobial therapy, or the geriatric problem which we now have as a result of advances in drug therapy. A *toxic effect* is the consequence of the agent's pharmacologic actions. It is one that is undesirable and a threat to normal physiologic function, if not a threat to life. It may be a consequence of a pharmacologic action that also provides the drug's therapeutic usefulness, or it may be associated with other facets of the pharmacologic properties of the drug. *Drug-induced disease* implies a response to the drug in which a disease results from its use.

Ocular structures can reflect all of these side effects. Within recent years, a variety of ocular changes has followed systemically administered agents. *Tranquilizers* such as phenothiazine derivatives have produced corneal opacities, cataracts, and retinal degeneration. *Steroids* have induced glaucoma and cataracts, predisposed the eye to infection, and caused edema of the optic nerve heads, simulating a brain tumor. *Antimalarials* and *anti-collagen* disease therapy also have produced retinal degenerations as well as corneal changes. *Sulfonamides* and *antibiotics* have produced inflammatory and atrophic disturbances in the optic nerve. *Vitamins* in excess, such as Vitamins A and D, can produce corneal opacities.

Agents instilled into the eye can produce undesired changes in the eye and elsewhere in the body. Steroids locally instilled can make glaucoma evident, possibly produce cataracts, and enhance viral, fungal, and bacterial infections of the cornea. Atropine and other cycloplegics may bring on an acute attack of glaucoma. Anticholinesterase agents repeatedly instilled into the eye may induce systemic signs similar to over-stimulation of the parasympathetic system. These are a few examples; many others are known. The hazards are evident. There is the possibility for disease states to occur because of the use of new drugs—so-called medical progress.

These effects must in part be considered as adverse, not just toxic. As a result of these reactions, however, it has been possible to determine hereditary patterns in reactions to drugs. Steroids raise intraocular pressure only in certain individuals. Not everyone shows these side effects with each drug. Is that because they have different enzyme systems for breaking down the drug? Or does the enzyme look the same biochemically but have a few differentiating characteristics?

It is important to avoid side effects, toxic effects, adverse effects, and drug-induced diseases by proper evaluation prior to releasing the agents for general use. This is not always possible. It is most important to find not only why some people react adversely, but what protects the majority against such action. This has led to a new branch of pharmacology called pharmacogenetics, which has been defined as the study of genetically determined variations in animal species that are revealed by the effects of drugs. This has given us insight into the nature of disease processes. Indirectly, side effects of drugs have aided medical progress.

# CLINICAL ASPECTS OF CATARACT

**John M. McLean, M.D.**
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Dr. McLean is professor of clinical surgery (ophthalmology) at Cornell University Medical College and attending surgeon in charge of ophthalmology at New York Hospital-Cornell Medical Center. He is also a consultant at seven hospitals in the New York metropolitan area.

Cataract is not a new problem. There is rather good historical evidence that operations for cataract were performed in the Bronze Age. With the possible exception of ritual circumcision, it would seem to be the earliest surgery on record. Today it is a problem of rapidly enlarging proportions as the old age segment of our population steadily increases.

What is cataract? Surely, everyone here knows that cataract is clouding of the crystalline lens — nothing less, nothing more. Many laymen are confused, thinking that a cataract is a growth, or film, anywhere from the cornea to the back of the eye, that is scraped or peeled off, or replaced by a corneal graft. Although we know better, we must remember that the general public may not, and that the word "cataract" without adequate explanation conjures up many bizarre notions.

What causes cataract? How is one formed? We wish we knew! We wish research were advanced to the stage that would allow us to understand the mechanism. Dr. Kinsey will address himself to this subject. We do know some of the causes, but we have not yet found out how they operate.

We know that babies may be born with cataracts. We know that some of these cases are on a hereditary basis. We need to know a lot more about the genetic mechanism at play. We know that some of these cases are the result of disease in the mother. The recent epidemic of German measles is a case in point. But how does it work? What can we do to avoid it? How does the baby happen to carry the live virus for so many months after birth?

We know that physical injury to the eye at any age may produce cataract. Our efforts here must be along the lines of accident prevention.

We know that chemical injury from certain drugs and industrial chemicals may cause cataract. This gives us some clues to research approaches. For example we know that injudicious use of drugs of the cortisone group may cause cataract and this points our thinking in certain endocrine and metabolic directions. We know that certain heavy metals may cause cataract and this encourages us to explore the enzyme systems that these metals may poison. We know that disturbances of sugar metabolism, diabetes for example, are associated with cataract formation. Many forms of "sugar cataract" are under experimental study today. These are interesting tools that open up vast areas for much more research.

We know that other endocrine diseases are accompanied by cataracts. We know that certain forms of radiant energy cause cataracts as well as physical trauma and chemicals. Is there a common denominator? How, in detail, do these things come about? We have to explore these areas and whatever paths research may uncover to get a more fundamental understanding of the mechanism of this condition which is blanking out the vision of so many people the world over. I have just come back from a visit to five of the continents. I can attest to the way ophthalmologists the world over are concerned with this growing problem and how they are looking to scientists of the United States to come up with some answers.

I have mentioned a few of the known causative agents, though we are quite in the dark as to how they act, but something like 90% of the cataracts we see are not associated with any of these factors. They would seem to be part of the aging process. What factors operate here? If we are going to keep more and more people alive longer and longer we must find out how to keep them seeing!

Clinically what can we do about cataracts until we can learn through an understanding of their mechanism how to prevent them, or medically how to reverse them? Our only recourse at the present time is surgical removal. This is admittedly a stop-gap procedure, but until we can learn more it is the best we can do. Cataract surgery, of one type or another, has been going on longer than recorded history and is still being improved. I know of no operation, be it simple appendectomy or the currently popular cholecystectomy, that has a higher batting average.

In recent years many technical improvements have made cataract surgery safer and more satisfactory. Advancements in suture techniques, improved instrumentation, operation under microscopic control are examples. Use of a particular enzyme, alpha chymotrypsin, has made it easier to free the cataract from its attachments and simplified the operation. At the same time this enzyme has introduced new complications, for it sometimes produces a complicating glaucoma. This may be a blessing in disguise for it may point the way to a better understanding of the mechanism of glaucoma itself, another of our major eye problems. In the last few years rapid freezing has been introduced as another means of taking hold of the cataract to get it out of the eye, safely, surely, and gently. This has already had much, perhaps too much publicity. These are only some of the recent advances in the surgical attack on a disease that we should learn to prevent, or, if it occurs, treat without operation.

What do we give a patient when we remove his cataract? Is his sight returned to normal? By no means. He has to wear heavy lenses to replace, somewhat inefficiently, the cloudy lens we have removed. Can he function again, visually? Yes, but not without many adjustments and considerable reeducation. There have been many recent improvements in cataract glasses, but they are far from restoring normal visual function. Contact lenses have been improved and come closer to restoring normal function, but they are not suitable for everyone, particularly the aged. Attempts have been made and are being made to replace the cataractous human lens by intraocular plastic lenses. This idea is a step towards more normal state, but not developed to a safe practical stage as yet.

So we have a condition which is interfering with the sight of an increasing proportion of our population that we can handle by surgery with a very high prospect of success. We must learn not only why it occurs, but how it occurs. We will continue to improve our surgical approaches and our optical rehabilitation, but this is not the ultimate goal. It should be the prevention, if possible, and the non-surgical treatment if not—all based on an understanding of the details of cataract formation, to be obtained through intensive research.

# LABORATORY RESEARCH ASPECTS OF CATARACT

**V. Everett Kinsey, Ph.D.**

*Kresge Eye Institute, Detroit, Michigan*

Dr. Kinsey is professor of ophthalmology and assistant director of research at the Kresge Eye Institute of Wayne State University School of Medicine. A Lasker Award winner, he is past chairman of the Association for Research in Ophthalmology and an editorial board member of *"Investigative Ophthalmology"* and *"Experimental Eye Research."*

A medical cure for cataract is *not* just around the corner, although the need for one increases annually since so-called senile cataract is the most common kind of all, and the average age of the population is increasing each year. But laboratory research probably offers the best bet. As Sidney Lerman[1] points out, it is rarely that one is able to obtain a fresh human lens from an individual suffering from a specific disease process that has not reached a stage of complete opacification. Such a lens is relatively useless with respect to studies on the activity of specific enzyme systems, metabolic pathways and other chemical aspects of lens physiology which might be expected to turn up leads, offering promise as a prophylactic or therapeutic agent for cataract.

While it may be hazardous to extrapolate from observations made on experimental animals to an apparently similar disease entity in man, the risk is probably not as great in the case of the lens as in other organs, because of the many similarities in metabolism, antigenic properties and mode of growth of lenses from different species.

In a majority of cases cataract in man is a part of the aging process. Wrinkled skin is too, but whereas progressive changes in skin have little but cosmetic effect on an aging person, ever greater opacification of the lens affects his whole psychologic, social and economic well-being.

In a lesser number of cases cataract is the result of degenerative processes brought on by developmental anomalies, intraocular diseases, genetic, metabolic disorders, toxic agents, radiations or trauma. It is with these kinds of cataracts that laboratory investigations have been chiefly concerned, and where hopefully, if the sequence of chemical events leading to opacification of the lens were sufficiently well understood, the greatest likelihood lies for developing a medical substitute for surgery.

Sugar cataracts have been studied most extensively in the laboratory, and serve to illustrate the direction of some recent investigations aimed at gaining a better insight into how cataracts develop. High concentration of glucose in the blood and aqueous humor is a characteristic of diabetes, high concentration of galactose, of galactosemia in infants who are born with a genetic defect in an enzyme concerned with sugar metabolism. Both conditions often lead to cataract and both are easily duplicated in the laboratory. In addition, feeding of xylose, another sugar, also produces cataract in experimental animals. Similarities in the appearance and histopathology of each kind of sugar cataract suggest that a common mechanism initiates the cataractous process. Two explanations have been proposed to account for how high concentrations of sugars cause the lens to become opaque.

The first hint as to the mechanism of sugar cataract came from the observation of van Heyningen[2] in England who showed that all three sugars, when present in high concentrations in the aqueous humor are converted by the lens to sugar alcohols. According to Kinoshita[3] it is the presence of sugar alcohols which sets off the sequence of events leading to lens opacification. He noted that the first pathologic sign in each kind of sugar cataract is the appearance of hydropic lens fibers caused by an accumulation of fluid which enters the lens by osmosis brought about by the hypertonic condition produced by the sugar alcohols. The swelling continues until the lens fibers rupture, disintegrate, and finally produce open spaces or clefts between them resulting in clouding of the lens, at first at the equator, and finally throughout its whole substance.

A second possible explanation for cataract, associated with high sugar and sugar alcohol concentrations, stems from observations made by Kinsey and Reddy.[4] These investigators showed that within hours after rabbits were made diabetic with alloxan, or within several days after rats became galactosemic by feeding them galactose, the concentration of free amino acids in the lens was reduced about 90%.

Could it be that lack of amino acids needed for resynthesis of proteins in the lens, causes it to become opaque? While definite conclusions cannot be drawn at present concerning the mechanism of cataract formation at the molecular level, the potential value of the experimental approach seems clear. For instance, a search might be made for an inhibitor of the enzyme which converts sugars to sugar alcohols, or appropriate supplemental feeding resulting in an increase in the amino acids in the blood might prevent or delay the appearance of these cataracts.

The need for further research, however, is obvious, and it is the chief purpose of this seminar to bring this point to the attention of the public, the ultimate benefactor.

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1. Sidney Lerman, M.D., C.M., Associate Professor of Ophthalmology, Assistant Professor of Biochemistry, School of Medicine and Dentistry, University of Rochester, Rochester, New York. "*CATARACTS: Chemistry, Mechanisms, and Therapy*," Charles C. Thomas, Publishers, Springfield, Illinois, 1964.
2. Antoinette Pirie, M.A., Ph.D., Margaret Ogilvie's Reader in Ophthalmology, University of Oxford, Fellow of Somerville College, Oxford, England.
3. Jin Kinoshita, Ph.D., Associate Professor of Ophthalmic Research, Harvard University Medical School, Boston, Mass.
4. V. Everett Kinsey, Ph.D., Professor of Ophthalmology, Assistant Director of Research, and D. V. N. Reddy, Ph.D., Associate Professor of Ophthalmology, Kresge Eye Institute of Wayne State University School of Medicine, Detroit, Michigan.

# THE USE OF THE COMPUTER IN THE STUDY OF EYE DISEASE

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Dr. Potts is professor of ophthalmology and director of ophthalmic research at the University of Chicago School of Medicine. He also is widely recognized for his work in biochemistry.

The most striking use of the computer in our research has been to sort out the part of the brain wave due to vision (Visual Evoked Response, VER) from the confusing welter of other brain wave material.

This has several useful consequences for the study of eye disease. First, since we are actually measuring brain waves we are sampling visual function some two-thirds of the way along the pathway to conscious perception. Other objective methods of measurement such as the electroretinogram (ERG) (eye waves) measure only the function of the very first stage of vision at the retina (the right sensing elements). Thus by combining both measurements we can objectively localize diseases of vision as being in the eye or being farther along in the visual pathway.

Second, the ERG is caused by a mass response to retinal cells, the response of a relatively few cells being difficult to detect. The area of the retina responsible for sharp vision—newspaper reading vision and automobile driving vision, not to mention rifle sighting vision and airplane piloting vision—is extremely tiny and its function is virtually undetectable by ERG. However, it is precisely this small group of retinal cells (the foveal cells) which connect with a very large number of brain cells, so that the brain wave response is much more preponderantly a foveal response and the latter can be detected by our method. Thus, with specially small stimulating lights we can measure objectively the function of this very tiny and very important part of the visual system.

One of the corollaries of being able to make such a measurement is the ability to determine whether an individual claiming loss of vision due to eye involvement does have actual visual loss. This method is effective in detection of malingering, and has significant medico-legal and insurance claim applications.

An additional application of the method has to do with the study of amblyopia (loss of vision) due to strabismus (crossed eyes). In our studies we have found uniformly that an adult with strabismus amblyopia has a diminished or absent response from the amblyopic eye only. This to our knowledge is the first demonstration that the end result of amblyopia is a physically measurable brain defect, although this has been suspected for many years. The technique with necessary modifications promises a method for measurement and detection of amblyopia in children too young to give any accurate subjective measure of vision. It also promises a method for following the effectiveness of treatment.

In contrast to this finding on strabismus amblyopia, our technique demonstrates that in hysterical amblyopia (loss of vision due to certain types of psychiatric disease) there is no such diminution, but normal or even super-normal response. These findings suggest that within the brain there are at least two separate stages between registration of sensation and its reaching consciousness. The first stage is affected in strabismus amblyopia and is amenable to measurement by our method. The second stage is involved in hysteria and prevents perception even though the first stage, measured by us, is intact. This suggests that we are approaching the point where electrical measurements will begin to tell us some specific things about consciousness.

Other computer applications to our research involve automated analysis of large amounts of data on the electroretinogram (eye wave) with enormous saving of technician time. Still another application is a study of information retrieval from the published literature by computer.

# CORNEAL RESEARCH INVOLVING:

## Phagicin—a New Type of Antiviral Compound
## Control of Donor Material for Keratoplasty
## Preservation of Living Corneas in "Suspended Animation"

**Herbert E. Kaufman, M.D.**

*University of Florida, Gainesville, Florida*

Dr. Kaufman is chief of the department of ophthalmology at the University of Florida College of Medicine. He is widely recognized for his work in finding the first antiviral agent successfully employed against infection in man in his use of IDU for the treatment of herpes simplex keratitis.

Despite our initial discovery of IDU as the first active antiviral agent, many problems remain in the treatment of ocular virus disease. The first problem is that better antiviral drugs are required. Ideally they should be drugs that are completely non-toxic and can be given systemically to penetrate the eye as well as other organs and to treat disease which is inaccessible to topical therapy. The second problem is that we are gradually learning that much virus disease is not caused by actively multiplying virus but may be caused by host hypersensitivity to virus products after virus multiplication has ceased. In disease caused by hypersensitivity, drugs which halt virus multiplication — antiviral drugs — cannot be effective, but rather a basic knowledge of the role of hypersensitivity in the causation of virus disease is required. Therapy will depend on the discovery of the basic nature of the antigens so that desensitization or neutralization of the antigens can be carried out, or will require the discovery of anti-inflammatory agents without the tendency of our present agents to reactivate late virus multiplication and make virus disease worse.

It should be clear that although the eye is involved in these studies, there is a search for systemically active antiviral compounds, as well as an attempt to understand some of the basic mechanisms of virus-caused disease in which hypersensitivity plays a major part. In both of these cases, the eye is a convenient and an important test organ, but in both cases, the findings may be of great importance to all of medical science.

### Phagicin — A New Type of Antiviral Compound:

In our laboratory, Dr. Ysolina Centifanto, in examining much of the older literature, recognized that other investigators had found weak and often irreproducible antiviral activity in extracts of certain bacteria. She thought that some of this antiviral activity might be due to the fact that these bacteria harbored temperate bacterial viruses that caused the bacteria to produce a substance with antiviral properties.

In order to study this phenomenon, one of the simplest and best studied bacterial virus systems was used. E coli, K12 strain, were infected with temperate lambda bacteria phage, a non-virulent phage which does not rupture the bacterial cell. It was found that in the process of infection of the bacteria by the phage, a unique substance was made which appears to be a small polypeptide. This substance, "Phagicin," is easily obtained and, with column chromatography, can be made relatively pure. It displays unique antiviral properties.

The antiviral spectrum of "Phagicin" is not completely known, but in tissue culture it completely suppresses herpes simplex and vaccinia viruses, DNA viruses, as well as Newcastle Disease Virus, an RNA virus. The spectrum of activity may be quite broad, but other viruses have not yet been tested. The action of "Phagicin" appears to be completely selective in that it can completely suppress the formation of virus plaques in infected cultures even when administered six hours after infection, acting to inhibit virus multiplication within the cell. In spite of this activity, however, it appears to have no detectable effect on the metabolism of the cell, and does not prevent immature cells from multiplying at an apparently normal rate. *In vivo*, it is clearly active in the treatment of herpes simplex keratitis, even when the disease is well established. Systemically in mice, it appears to be non-toxic and early experiments suggest that it has potent systemic antiviral activity, although more studies are required.

Although much remains to be learned about "Phagicin," its origin is unique, being made by bacterial cells, and its antiviral activity appears to be quite selective and specific. Its *in vivo* activity has been confirmed in the treatment of ocular disease, and activity appears present in the treatment of systemic disease also. This unique antiviral substance is a totally new type of antiviral compound which is not an antimetabolite and appears not to interfere with the normal cell. The importance of the discovery of this type of compound seems great, whether or not this particular agent is used in the treatment of human disease.

### Mechanism of Virus Disease:

The advent of antiviral drugs which stop virus multiplication has made it suddenly obvious that active multiplication of virus is not responsible for all visible virus disease. This first became apparent in ocular disease in which we found that disciform keratitis and iritis were more common in animals which were immune to the virus infection and later re-infected. This effect is not limited to the clouding of the cornea seen with disciform keratitis, however, but there is good evidence that the cutaneous reaction to vaccinia occurs after the virus has completed its multiplication and its hypersensitivity response to the virus. Similarly, in mice, death from lymphocitic choriomeningitis virus appears to occur because of host sensitivity to the virus, and mice which do not develop hypersensitivity, do not die although the virus continues to multiply normally.

In our laboratory, Mr. Robert Lausch and Mr. Jerry Swyers have clearly documented that skin lesions occurring after herpes simplex infection as well as eye lesions identical to disciform keratitis, are a response of delayed hypersensitivity to partially purified virus antigen. Although no virus is present, skin lesions and ocular lesions can result from the injection of this antigen in sensitized animals. This type of reaction histologically is a delayed hypersensitivity reaction both in the skin and in the eye, and it can be transferred by cells but not by serum.

Herpes simplex infection of the eye is a prominent cause of blindness and prolonged misery, and the hypersensitivity phenomena associated with the virus disease appear to be a major cause of the disease which is seen. The demonstration of the importance of virus induced hypersensitivity has implications in clarifying the mechanisms of other types of virus disease. Continued success in the identification and purification of these antigens may make possible not only a better understanding of disease, but the possibility of neutralizing or destroying the extracellular antigens through the use of selective enzymes or other agents.

### Control of Donor Material for Keratoplasty:

There is reason to think that the failures of some corneal transplants may be due to donor tissue which is abnormal, but its abnormalities cannot be detected by the usual methods. We have developed stains to visualize the corneal endothelium in the intact cornea, and find that, in fact, in tissue from older persons a significant proportion (up to 25%) may have early endothelial dystrophy or other abnormalities. These studies have included tissue from several hundred "normal" eyes that would otherwise have been used for keratoplasty, and the use of such a technique, specially in the older age group, may be a significant advance in improving results of keratoplasty.

### Preservation of Living Corneas in "Suspended Animation" at —190°C:

For penetrating keratoplasty, tissue must be alive. This has meant that it must be used within forty-eight hours after death. The difficulty in matching patient, surgeon and tissue at the same time has resulted in much wastage of tissue, and the lack of available tissue for certain emergencies. In addition, in many parts of the world, Eye Banks cannot be established and tissue is not available. One of the difficulties of developing a method of preserving corneal tissue alive has been the determination in human tissue of whether cells are alive or dead. When cells are injured by freezing, the enzymes leak out upon subsequent incubation. The number of cells preserved intact can be quantitated, and the staining of cellular enzymes permits a rapid quantitative test to cellular viability. With this test we have developed a technique of freezing living tissue with dimethylsulfoxide, albumin, and sucrose at a precisely controlled rate to —190° and keeping this tissue alive in a state of "suspended animation." This living preserved tissue provides corneal transplants in animals which remain clear, and we have recently finished a large comparative study in El Salvador in which living preserved tissue has been compared with fresh tissue that we shipped to El Salvador from Eye Banks all over the United States. Results to date indicate that the preserved tissue is as suitable as fresh tissue for penetrating keratoplasty and that such a technique of preservation may permit corneas to be available all over the world as needed.

# GLAUCOMA

**Bernard Becker, M.D.**

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Dr. Becker is head of the ophthalmology department at Washington University. His work has appeared in more than 150 publications in the field of eye research and vision disorders.

### Summary

Topical corticosteroids raise intraocular pressure and induce a clinical picture identical with primary open-angle glaucoma. This effect is noted not only in patients with known primary open-angle glaucoma, but also in their close relatives. Evidence has been accumulated to support the hypothesis that this most common form of glaucoma is recessively inherited, and that topical corticosteroid testing permits the recognition of the carrier (heterozygous) as well as the glaucomatous (homozygous) states.

### Significance

The finding that topical corticosteroids will raise intraocular pressure to dangerous levels in some individuals has obvious clinical implications, such as avoiding the indiscriminate use of the drug, limiting the dose and duration, and following the intraocular pressure closely in all patients subjected to such medication. In addition, these findings have led to an intensive search for agents with corticosteroid activity that can be used topically without inducing elevations of intraocular pressure. Two such agents are now under active investigation and early results are promising.

Of much greater significance are the fundamental implications of identifying the genetic state of the individual by means of topical corticosteroid testing. If the hypothesis proves correct, we can recognize the potential glaucoma patient before any spontaneous defect in outflow facility or intraocular pressure can be detected. This makes it possible to follow the hereditary defect through families and trace the transmission of the disease. One can also recognize heterozygous carriers of the gene who may show borderline pressures on occasion but do not develop the disease. By early recognition of potential glaucoma patients, one may not only learn how the disease develops and produces damage, but also determine the fundamental biochemical defect. Of much practical importance will be the recognition of those factors which suppress or delay appearance of the overt disease in individuals genetically destined to develop glaucoma.

### Background

Primary open-angle glaucoma is a painless elevation of intraocular pressure which produces damage to the optic nerve without warning symptoms. This potentially blinding disease is genetically determined, but demonstrates an increasing incidence with age. It is estimated that some 2% of the population over the age of forty have this disease. In groups of people over the age of sixty-five, surveys have demonstrated an 8-10% prevalence. When unrecognized and untreated, the disease is progressive, resulting in loss of field and even blindness. A variety of very effective therapeutic agents have become available in recent years. When properly treated, vision may be preserved for the lifetime of the individual. Therefore, emphasis has to be placed on early recognition of glaucoma and its prompt control by adequate therapy.

### Early Recognition

It has become possible to recognize glaucoma much earlier because of better methods for measuring intraocular pressure (such as the applantation tonometer of Goldmann). In addition it is now possible to measure the impaired outflow of fluid from the eye even before there is pressure elevation (tonographic method of Grant). As indicated above, with topical corticosteroids one may induce pressure elevations in some individuals who have not yet demonstrated any other signs of the disease.

### More Effective Therapy

With increased understanding of the nature of the glaucomatous defect (obstruction to outflow) and the role of secretion in maintaining intraocular pressure, newer therapeutic agents have become available. These include drugs which improve the impaired outflow facility (parasympathomimetic, anticholinesterase, and adrenergic agents), and those that partially suppress the secretion of aqueous humor (epinephrine and carbonic anhydrase inhibitors).

### Techniques

The methods used have included the measurement of intraocular pressure by applanation and Schiøtz methods, the measurement of outflow facility by tonography, the administration of corticosteroid drops to one eye only using the opposite eye as a control, the use of water drinking provocative tests, the careful observation of patients with the slit lamp and ophthalmoscope, and the repeated measurements of visual fields with the Goldmann perimeter.

# PROGRESS IN CURRENT RESEARCH IN THE DIAGNOSIS AND TREATMENT OF OCULAR TUMORS

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In ophthalmology, we have a good opportunity to observe the effects of different modalities on various types of tumors. Tumors implanted into the anterior chamber and into the vitreous can be watched accurately through the transparent media by magnifying lenses. Various investigators, therefore, are using the eye as a medium for watching the effects of therapy and this is true especially in regard to chemotherapy.

Malignant tumors encountered in ophthalmology [melanoma, neuroblastoma (retinoblastoma), rhabdomyosarcoma, lymphoma, etc.] give a better prognosis than similar tumors elsewhere because they are overt and therefore diagnosed earlier. Also, those that affect the interior of the eye give early evidence of their presence either from loss of visual function or because they can actually be seen.

A melanoma of the choroid and ciliary body, the commonest malignant tumor in ophthalmology, usually gives subjective evidence of its presence in the form of visual defects. The next most frequent malignant tumor is retinoblastoma – a member of the tumor family of neuroblastoma – one of the more common cancers affecting children. A reflex of this tumor is usually seen by the parent through the pupil. Although the affected eye must be enucleated, examination of the fellow eye usually leads to the diagnosis of early curable cancer. Tumors in the orbit are apprehended early because of obvious unilateral exophthalmos and/or double vision. As a result, even such a highly malignant tumor as rhabdomyosarcoma, the commonest malignant orbital tumor in children, has a relatively good prognosis when prompt adequate surgery is elected. Therefore, the overt nature of ocular cancer, in contrast to the occult nature of cancer elsewhere in the body, explains the early diagnosis which is reflected in the mortality rate. For instance, the overall cure rate of choroidal melanoma is 50 per cent, of early retinoblastoma—85 per cent, of early orbital rhabdomyosarcoma—50 per cent, and of orbital lymphomas—about 50 per cent. These figures highlight the importance of early diagnosis in the cure of all cancer.

Of the four types of cancer which most often manifest spontaneous regression and cure, two of these (melanoma and neuroblastoma) are the commonest malignant ocular tumors. Therefore, in ophthalmology efforts are being made to take advantage of this opportunity to study host resistance or auto-immunity. This assumes greater importance now as we know cancer cells commonly reach the blood stream. In some persons, circulating cancer cells remain viable and grow (metastasize), but in most they don't. Why?

Retinoblastoma occupies a unique position as the only truly malignant human tumor with definite hereditary characteristics (autosomal dominant gene). Forty-two per cent of the survivor's progeny have retinoblastoma. So dominant is this trait that sterilization or abortion seem justified in the case of a survivor. The medical profession is often derelict in failing to advise the parents or the patient against having children. One reason that there is a failure to counsel a survivor regarding the heredity of the disease is that the treatment for retinoblastoma occurs in infancy or early childhood with a long latent period before the marriageable age.

Statistics indicate that the frequency of retinoblastoma has shown a steady increase from 1 in 34,000 in 1931 to 1 in 14,000 births in 1961 (François).[*] Factors to be reckoned with in this increase are lower mortality rate, i.e., more adult survivors produce affected offspring, and improvement of investigation and diagnosis.

Let us assume that 70 per cent of these children, if handled carefully, will now survive and that social and other factors will limit the production of these survivors to half the normal rate. The net reproductive expectation at birth of any person with retinoblastoma will then be 35 per cent of normal. This change in recent decades from virtually zero to 35 per cent will bring a commensurate change in the frequency of the responsible gene. If the mutation rate is $2 \times 10,^{-5}$ then in eight generations or so, retinoblastoma will occur half again as frequently as it does today. To extend the speculation further, if we can some day save all patients with this disease and enable them to reproduce at the normal rate, retinoblastoma will become the normal characteristic as the result of constant mutation pressure, and individuals without the disease will be the exceptions. While this is highly unlikely, it does suggest that as control of neoplastic and other lethal disease is added to the conquest of infection, genetically determined disease will play an increasingly significant role in the development of mankind.

Therefore, we have here an excellent opportunity to study the chromosome pattern and the role heredity plays in cancer.

The tumor first manifests itself as a whitish cat's-eye reflex in the pupil. It has multicentric origins in one or both eyes (two-thirds are unilateral and one-third bilateral); 84 per cent are multicentric in one eye alone. When the disease involves only one eye, enucleation is almost categorically advised and, if performed before metastasis or extraocular extension has occurred, enucleation proves curative. If both eyes are involved, the eye with the more advanced tumor is removed and treatment is directed to the remaining eye.

An analysis of the histories of 235 consecutive patients with retinoblastoma showed that in 25 per cent of all the cases the diagnosis had been incorrect in the beginning, and that in 20 per cent of all the cases the diagnosis was delayed for a period ranging from two months to two years.

The treatment of patients with retinoblastoma has been improved tremendously over the past decade or more. Chemotherapy has been of more help in the treatment of this type of cancer than in any other. With chemotherapy supplementing betatron radiation and sometimes light coagulation, the cure rate in the favorable cases is 85 per cent. This means cure of the cancer with preservation of normal vision.

A unique feature of retinoblastoma is that the host tissue (the retina) is transparent and that this white opaque tumor can not only be viewed accurately through transparent media (cornea, aqueous, lens, vitreous) but can be magnified from two to ten times with the ophthalmoscope. This affords not only accurate diagnosis, but accurate observation regarding treatment effectiveness. Therefore, we believe we can say with reasonable certainty when a tumor is not responding satisfactorily and when a cure has been accomplished. After six months a cure can be predicted (we have had only a few exceptions).

The diagnosis of retinoblastoma can be difficult because the commonest way in which this tumor is detected is through the occurrence of a white reflex in the pupil, and there are other conditions which reflect rays of light in a similar manner and must be differentiated from retinoblastoma. Refinements in diagnosis have led to better diagnosis and early detection of this tumor.

Among the refinements in the diagnosis of intraocular tumors in general, the following adjuncts can be mentioned: foremost is that of indirect ophthalmoscopy, slit lamp contact lens funduscopy, the fluorescein test, ultrasonography — which in the diagnostic field is being explored both in a qualitative as well as in a quantitative way. Ultrasonography may also prove of help as a destructive measure in the treatment of intraocular tumors. Further diagnostic aids are the isotope uptake, and perhaps infrared scanning may be helpful in diagnosing intraocular tumors just as it has been in the diagnosis of breast tumors. All of these aids in earlier diagnosis lead to earlier treatment which is reflected in the cure rate and the prognosis.

More fundamental basic knowledge and accurate classification are leading to the recognition of certain lesions, and saving eyes formerly subjected to unnecessary enucleation. Many eyes which had been removed with the diagnosis of a malignant melanoma in fact had a melanocytoma of the disc, which is recognized now as a benign and harmless tumor. Melanomas of the iris were formerly put in the same category as malignant melanomas elsewhere, and radical surgery led to the loss of many eyes. Now it is appreciated that these lesions in the iris are not metastasizing but may be locally infiltrative. Therefore, local excisions, including iridocyclectomies, are currently carried out and many eyes are saved. Also, hyperplasia of the pigment epithelium of the choroid leads to a tumor which in the past has been confused with malignant melanoma, resulting in unwarranted enucleation. Hemangiomas of the choroid in the past have been most difficult to diagnose, and a better understanding of these now has saved many eyes from removal. In past years, removal of the eye and orbital contents had been carried out because of a lesion which was then thought to be a malignant tumor of the orbit and is now recognized as a pseudotumor which does not require radical surgery. Also, it is appreciated that a surprising number of children have granulomas of the eye which are due to a larval infestation contracted from dogs and other animals that have intestinal worms. We realize more and more that owning pets is not entirely without hazard. Two well recognized eye diseases now are contracted through the association with animals, the one is larval granuloma and the other toxoplasmosis. Another condition which has a good prognosis but which has simulated malignant tumors is the so-called juvenile xanthogranuloma.

A better understanding of the pathology and clinical course of orbital tumors is leading to more accurate diagnosis and more effective treatment. Also, the operative technique of approaching orbital tumors is being constantly improved.

In conclusion, it can be said that our knowledge in every aspect of ocular oncology has progressed to the point where most of our tenets of 10-20 years ago are now passé. The current pace indicates that comparable or even greater progress will be made in the next decade.

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*François, J. 1962. Data on the heredity of retinoblastoma. Given as part of a symposium *"New and Controversial Aspects Concerning Ocular and Adnexal Tumors"* sponsored by Division of Ophthalmology, Baylor University College of Medicine, Houston, Texas.

# FLUORESCEIN IN THE STUDY OF BLOOD FLOW TO THE EYE

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Dr. Norton is chairman of the ophthalmology department at the University of Miami School of Medicine. He also is chairman of the visual sciences study section of the National Institute of Neurological Diseases and Blindness, Bethesda, Maryland.

Since the invention of the ophthalmoscope in 1851 man has been able to visualize the retinal blood vessels and determine changes in appearance, calibre and course. With the presentation of the ophthalmodynometer in 1917 man was able to determine the approximate blood pressure in the central retinal arteries. These studies told little about the rate of flow in the individual vessels nor the permeability of these vessels.

In 1961 the introduction of serial photography of fluorescein in the circulating blood made available a new method to study and permanently record function and structure in the living eye. Detailed morphology and function of the vasculature of the optic nerve, retina and choroid unappreciated by ordinary ophthalmoscopy was brought out with remarkable clarity.

## Technique

Fluorescein is one of many compounds which absorbs light at one wave length and remits part of this light as fluorescence, at a longer wave length. By the use of appropriate filters one can illuminate the retina with blue exciting light and then by placing an appropriate filter in front of the camera cut out the reflected blue light but transmit the emitted fluorescence (green-yellow light). Ideally, then, only the fluorescent light reaches the film.

By adapting a high speed rapid sequence camera, or moving picture camera, the behavior of the dye as it passes through the ocular circulation is recorded.

*Normal.* Some of the important normal changes noted are:

1. Clear demonstration of the individual variations in the blood supply of the optic disc and retina.
2. Difference in type of flow in the arterial and the venous systems and the effect of vessel crossings on flow.
3. Variations in circulation time within the different regions of the retina.
4. Variations in the visible choroidal pattern due to variations in the pigmentation of the individual.

*Abnormal.* The important question is how have variations in these patterns helped in the recognition and management of disease?

1. In the differential diagnosis of ocular tumors one finds a different pattern when malignant melanomas are studied in contrast to naevae, hemorrhagic lesions, and metastatic tumors. This enables the ophthalmologist to make a more accurate diagnosis resulting in fewer eyes being enucleated for non-malignant tumors.
2. In the study of diabetes one may recognize advanced changes in the permeability of the retinal capillary system and yet have difficulty recognizing any anatomical changes in the retina. This may open new doors to the early detection of diabetic retinopathy and to the early evaluation of the effect of new treatments (such as hypophysectomy) on the retinal vessels of the diabetic.
3. In the study of macula disease one is able to incriminate either the retinal vessels or the choroidal vessels as the forerunner of the disease process. In the great majority of cases the retinal vessels remain normal without any change in permeability while the choroidal vessels can be shown to leak fluorescein under the pigment epithelium and retina. Thus, one can be sure this is usually a disease of the choroid and one can often locate the area of disease in the choroid. The possibility of treating these areas with photocoagulation is immediately evident.

   In some cases of macular disease, especially that seen after cataract surgery, one can demonstrate that the disease is confined to the retina and its vessels. So far this has not helped in the therapy but it does focus our attention on a much smaller area and should lead to an earlier solution of the problem.
4. In the study of variation of retinal flow time such as seen in carotid artery disease and occlusive disease of the retinal vessels, one can, sometimes, demonstrate the location of the block, the completeness of the block and evaluate the therapeutic response.
5. In the study of collateral circulation one can observe and record the development of the new channels. Do these represent new growth or the opening up of previously unutilized channels?

## Other Approaches to the Study of Blood Flow to the Eye

Blood flow is also being studied by *implanted flow meters* on the ophthalmic artery; variations in *reflected light* from the ocular fundus, and a study of *radioisotopes* as they pass through the ocular tissue. As these develop they will give more quantitative information on blood flow to the eye and therefore a better understanding of the role played by changes in blood flow in the development of retinal and choroidal disease.

*Cannulation-perfusion* techniques are being carried out at Georgetown and if successful they could lead to isolation of the eye so that it could be perfused by antimetabolites or other specific therapeutic agents. This technique could be helpful in the treatment of uveitis, ocular tumors, infections.

## Eye Banks

One usually thinks of corneal transplants when one discusses Eye Banks. However, one of the major contributions eye banks have and will make is in the study of ocular pathology. Most ocular diseases have had little pathological correlation because they do not result in death. With the large volume of material obtained through eye bank efforts the door to correlation of anatomical changes with clinical changes has been opened. This has been particularly fruitful in the study of choroidal and retinal blood vessels.

# DIABETIC RETINOPATHY

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Dr. Patz is assistant professor of ophthalmology at the Johns Hopkins University School of Medicine, and ophthalmologist at the Johns Hopkins Hospital. He is internationally known for his successful studies in retrolental fibroplasia for which he has received the Lasker Award and numerous other honors. He is also surgeon at the Baltimore Eye and Ear Hospital and attending ophthalmologist at Sinai Hospital of Baltimore.

### Summary of Work and Introduction

Diabetic retinopathy is the retinal disorder produced by the changes in the blood vessels of the retina that frequently develop in long-standing diabetes. Approximately 45,000 persons in the United States are legally blind from diabetes and retinopathy accounts for their major visual damage.

One of the major obstacles in the study of diabetic retinopathy has been the failure to find an experimental animal that developed retinopathy. We have observed (1962) that dogs with diabetes may develop retinopathy typical of early retinopathy seen in human diabetic patients. This represents the first opportunity to study experimentally this serious ocular complication of diabetes and opens new areas for investigation.

### Significance

Approximately one percent of the population in the U.S. (two million persons) has known diabetes at present. Through better control of infection and other complications the longevity of diabetic patients will probably increase; hence, a greater number of patients will be afflicted with retinopathy.

Methods of treatment that are thought to be possibly beneficial for the patient with diabetic retinopathy can be tested in diabetic dogs. The finding of retinopathy in dogs will permit specialized studies, frequently not possible in human patients, aimed at clarifying the basic causes of diabetic retinopathy.

### Background

Considerable progress in our understanding of the problem of diabetic retinopathy has been made in the past two decades. The late Doctor Jonas Friedenwald of the Wilmer Institute, Baltimore, and Doctor Norman Ashton, Institute of Ophthalmology, London, England, in the 1940's demonstrated the important role of the balloon-like enlargements of the retinal capillaries (aneurysms) and their frequent association with similar lesions in the kidneys of diabetic patients. Doctors Bernard Becker and Stanley Coleman, Department of Ophthalmology, Washington University, St. Louis, in 1962 demonstrated with the use of a fluorescein-labelled insulin that the retinal aneurysms and kidney lesions showed a similar reaction in the diabetic. In the 1960's Doctor J. M. B. Bloodworth, Jr., Department of Pathology, University of Wisconsin, and investigators elsewhere found that the thickening of the retinal capillary wall (basement membrane) that occurs in diabetic retinopathy is a part of the generalized alteration in the capillaries that has been recently described throughout the body in the diabetic.

Many investigators have observed that the incidence of diabetic retinopathy was usually directly related to the duration of diabetes. For example, in those patients with diabetes for 15 years, 70% show retinopathy and in those with diabetes for 25 years approximately 90-95% show some degree of retinopathy. Fortunately, many of these patients with milder retinopathy maintain useful vision.

In 1960 Doctors David Cogan and Toichiro Kuwabara of the Howe Laboratory, Boston, developed a new technique of digesting away the nerve substance of the retina leaving the blood vessels undisturbed. This method permitted for the first time a detailed study of the cells contained in the wall of the retinal capillaries. These investigators discovered that a selective degeneration of the cell enclosed in the capillary wall occurred in diabetic patients. From their observations they postulated the "Shunt Theory" of diabetic retinopathy.

There is suggestive evidence that diabetic retinopathy may be influenced by growth hormone from the pituitary gland. Doctor Bloodworth and co-workers, and Doctor H. R. Hausler and associates, Ophthalmology Department, University of Toronto, have recently found that dogs rendered diabetic by growth hormone may develop retinopathy similar to that previously observed in our natural diabetic dogs. Doctors Tom Merimee and Thaddeus Prout, Department of Endocrinology, The Johns Hopkins Hospital, have recently shown that the output of human growth hormone is strikingly influenced by the metabolic condition of other endocrine glands. Further study of the control of this hormone will be important in patients with diabetic retinopathy. There is no generally accepted therapy for most cases of diabetic retinopathy; however, hypophysectomy (removal of the pituitary gland) appears very promising in certain carefully selected cases.

### Techniques

Our study will primarily concern dogs who develop natural or spontaneous diabetes. We proposed to investigate our diabetic dogs by the following methods:

(1) The retinal blood vessels will be examined by the digestion technique of Doctors Cogan and Kuwabara.

(2) Biochemical studies on the retinas from diabetic and control non-diabetic dogs will be compared.

(3) The blood vessels of the retinas will be studied with the high magnification of the electron microscope.

### Human Interest

In a recent survey we found that most owners on learning that their dog had diabetes attempted treatment. The daily injection of insulin and frequent checking of samples of blood and urine for sugar presented many serious problems and considerable expense so that within a few months most owners requested that euthanasia be performed.

It would be helpful if these dogs, instead of being destroyed, could be contributed to our colony of diabetic dogs at the Wilmer Eye Institute of The Johns Hopkins Hospital. This colony has been maintained for the past three years under the close supervision of our consulting veterinarian. The dogs are housed in a special facility where their diabetes is regulated in the same manner as human diabetic patients are treated. The dogs are given a prescribed amount of exercise and outdoor walks daily. All of the diabetic dogs in this colony are pet animals and they have been cooperative subjects for periodic examination of their eyes with the ophthalmoscope. These observations may be ultimately useful in the treatment of human diabetes.

*Associates:* Joseph W. Berkow, M.D. and A. Edward Maumenee, M.D.

# RESEARCH IN RETINAL DETACHMENT

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In order to produce a retinal detachment, two conditions must be fulfilled: (a) a hole must exist in the retina and (b) the vitreous must be fluid in the area of the retinal hole. The fluid vitreous passes through the hole, under the retina, and floats it off the choroid. The retina is then deprived of its blood supply and becomes insensitive to light. Repair of a detached retina consists in (1) detecting by ophthalmoscopy all the retinal breaks present and (2) closing them by surgery.

Three areas of research will be discussed: (1) the causes of retinal detachment, (2) progress in ophthalmoscopy and (3) progress in surgery.

**(1) Present concept of causes of retinal detachment.**

Retinal detachment is the result of a combined process: (a) First, weak areas exist in the retina of many people. Recent work indicates that perhaps as much as 6% of the population without eye complaints has little holes in the retina. These result either from tiny anomalies in development of the tissues of the eye or from localized areas of damage to the retina caused by a localized and asymptomatic disease process (like peripheral uveitis or lattice-like degeneration); (b) second, superimposed on the above is aging which further weakens the weak spots in the retina and causes syneresis (liquefaction) of the vitreous gel. The aging process provides the fluid to float off the retina. It also causes shrinkage of the remaining vitreous gel. This causes traction on the retina, pulling it off the choroid and causing additional retinal tears.

Trauma is a definite cause of retinal detachment in about 16 per cent of the cases. In the absence of retinal breaks, indirect trauma (a fall, a blow on the head) almost never causes a retinal detachment. It takes a direct blow on the eye to cause a tear of the retina followed by detachment. The mechanism by which the eye is damaged in such cases has been elucidated by F. Delori, a physicist of the Retina Foundation.

A clear understanding of the causes of retinal detachment leads to important conclusions relative to preventive treatment. Obviously not all subjects with a break in the retina (6% of the population without eye complaints) should be operated on preventively. Cases for preventive surgery must be carefully selected among those who show breaks in the retina. Full agreement has not yet been reached as to the best methods of selection.

**(2) Progress in ophthalmoscopy.**

Detection of retinal breaks is done with an ophthalmoscope. With ophthalmoscopes currently used, however, it is often difficult to find all the retinal breaks. A new ophthalmoscope has corrected this deficiency. It is binocular, easy to handle, and permits one to see the full extent of the retina provided that the patient's pupil is dilated. Previous instruments permitted one to see clearly only about two-thirds of the retinal area.

In recent years, Oleg Pomerantzeff, a physicist of the Retina Foundation, demonstrated that an even better instrument could be made to see binocularly the retina of a patient whose pupil is no larger than 1 mm in diameter. A pilot model of this new ophthalmoscope was designed and built after all its optical and mechanical elements had been optimized.

Many of the problems arising in ophthalmoscopy result from the fact that one wants to see with both eyes through the patient's small pupil. At the same time a light must be projected through the pupil. In passing through the cornea, the light causes a strong reflection which must be avoided by the observer's eyes. This is accomplished by separating the path used for the light beam from the paths used for visualization by the observer's two eyes.

If the corneal reflection could be suppressed, the problem of ophthalmoscopy would be considerably simplified. Pomerantzeff is currently attempting to produce an interferential filter which would be placed on the front surface of a contact lens, on the patient's eye, and would suppress the corneal reflections. At this point high speed computation has indicated the best method of making such a filter. It is necessary to refine the techniques for producing interferential filters before it is possible to make the filter exactly as computed.

Another problem of ophthalmoscopy is that only a small portion of the fundus can be seen at any one time. For rapid and accurate scanning of the eyes of many individuals, it would be desirable to see the whole retina simultaneously. The problem consists in devising a method for seeing over 180° of the inside of a sphere through a tiny hole (the pupil). Computation has shown that this was indeed possible. Pomerantzeff foresees that mathematical modelling on high speed computers will revolutionize our methods of ophthalmoscopy within five years. The inside of the human eye will be examined binocularly, without reflections, and 180° of field will be visible simultaneously. It will also be possible to record this panoramic image either on still film or on movie film. Color movies of the fundus have already been taken through a method devised by Stenstrom, medical illustrator of the Retina Foundation. So far, these movies encompassed a small field of the fundus.

The final stage of the improvements under investigation will delight all the patients. The light now used for fundus examination is as strong as tolerable to the patient. In the future a very dim light will suffice. A good photograph of the fundus has been taken in our laboratories, although it was illuminated by a light too dim to be seen with the unaided eye. The image obtained was enhanced by photomultipliers and then photographed.

**(3) Progress in surgery.**

The aim of any operation for retinal detachment is the permanent closure of the retinal breaks. One must, therefore, irritate the choroid to produce a scar in it and then evacuate the subretinal fluid in order to permit the retina to reapply itself to the choroid.

*A. Irritation of the choroid.*

The method most commonly used to irritate the choroid is surgical diathermy (a high frequency alternating electrical current) applied to the sclera over the areas of the retinal breaks. Recently equipment was developed for freezing small areas of the choroid instead of burning them with diathermy. This procedure is often gentler and safer when the sclera is in bad condition, as in reoperations.

There are many cases where the retina

does not readily come in contact with the choroid, because the vitreous is abnormally adherent to the retina and has shrunk. Two types of methods have been developed to correct this: scleral buckling and vitreous injections.

*B. Scleral buckling procedure.*

Scleral buckling is a procedure in which a hump is made in the sclera by implanting material in it. The hump must be located in the area treated with diathermy. Its purpose is to bring the treated choroid and the detached retina in contact. The material used for making the hump is either absorbable (fascia lata, collagen) or non absorbable (silicone rubber). A scleral buckling may be made permanent by using non absorbable material maintained in place by sutures and by a silicone belt placed around the eye. When no belt is used or when absorbable material is utilized a temporary buckle results. The most important effects of scleral buckling are (1) it has reduced the hospital stay for a retina operation from 30 to about 6 days; (2) the patient may be mobilized the day after operation and does not need pinhole glasses; (3) percentages of success have risen from about 65% to about 85%.

*C. Vitreous injections.*

Vitreous injections are used to push the retina back against the choroid. Materials employed are water, air and silicone oil. Recently, at the Retina Foundation, efforts have been made to make human reconstituted vitreous starting with elements found in the umbilical cord. This would permit to replace the diseased vitreous by real vitreous gel instead of substitutes.

*D. Photocoagulation.*

Photocoagulation is a method by which a powerful narrow and parallel beam of light is sent through the patient's pupil. It forms an image on the retina where it creates a burn. This permits to cause a scar in the retina and choroid without surgical incision. The beam of light used is obtained either with a xenon arc or with a ruby laser. The initial enthusiasm for ruby lasers is now gradually subsiding because it becomes more widely recognized that a xenon arc source is safer and more effective for photocoagulating the eye than a ruby laser.

Photocoagulation is the method of choice to seal retinal breaks when no subretinal fluid is present. If the transparent media are not clear (due to incipient cataract for instance) photocoagulation cannot be used safely. Then, cryo applications can often be used without incision, instead of photocoagulation.

# SCANNING PATTERNS OF THE EYE

**Derek H. Fender, Ph.D.**

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Dr. Fender is associate professor of biology and electrical engineering at the California Institute of Technology. Born in England, he came to America in 1961 to pursue his major research interest in biological systems analysis, the application of stabilized retinal images and other experimental techniques to human visual perception.

Summary:

The human eye is rarely still; it normally moves, directing the gaze from one point to another in the visual scene. As a result, the image formed on the retina is continually moving over the light receptors. We do not, however, perceive a blurred image such as is produced by moving a camera during the exposure. The experiments described in this paper show that the sharpness of our vision depends on eye movements and that without them most of our visual acuities are reduced.

In our every day life, the eyes play a most active part. Except when we are asleep we use them constantly and they are forever glancing from one place to another gathering information from the world around us. However, the way our eyes move is not the haphazard process it might seem to be. It follows a more or less regular sequence. In the past years many people have investigated the patterns of eye movements for all sorts of different reasons. There is the artist who designs the layout of advertisements and is interested in the way our eyes scan a scene; for if he knows how the eyes normally examine a picture then he can place the most significant part of the advertisement in a position at which we are most likely to look. Or a little item like the price can be hidden away in some corner which is not normally explored by our eyes.

The designer of the instrument panel of a modern aeroplane faces a similar problem but for another reason. Some of the meters are very important and are continually referred to by the pilot whilst in flight; others are less important, so they are arranged on the panel in such a way that the pilot can look quickly and easily at most of the instruments without being unduly distracted from his main job of flying the aeroplane. Again, in this case, knowledge of the normal pattern of searching movements made by our eyes enables the designer to position the instruments to the best advantage.

Various methods have been used at one time or another for measuring the movements made by the eyeball. We provide each of our subjects with a tightly fitting contact lens which is moulded in perspex to fit the eyeball very accurately and to follow its movements quite faithfully. There is a small stalk attached to the lens, and this stalk carries at its end a miniature mirror.

A beam of light from a projector is reflected from the mirror attached to the contact lens on to a screen and movement of the beam can be recorded photographically. If the eyeball moves then the spot of light dances around on the screen; quite small movements of the eyeball produce large movements of the spot of light. The movement is so sensitive that rotation of the eyeball as you transfer your gaze from one side to the other of a hair held at about arm's length can be detected.

Such a mirror, together with a simple projection system and a photographic plate, provides a record of how the eye examines a scene. The subject's eyes wander over the picture, hovering selectively at certain points. The mirror moves with the direction of gaze, reflecting the beam of light, which builds up exposures at corresponding points on the photographic plate. When the resulting negative is printed, the spots of light outline the object that was being viewed and the relative amounts of visual attention accorded to various areas.

What happens when a subject tries to fixate as closely as possible on a small stationary target? We find that his eyes continually drift off target but from time to time he corrects these drifts with jerks; these movements we call flicks or saccades. In addition to these motions each eye performs a small tremoring motion—it vibrates slightly as it moves to and fro. This tremor is just about the right size to move the image on the retina (the sensitive layer of light receptors at the back of the eye) from one receptor to another. We believe that this tremor is the most important of all the eye movements.

The problem we set out to solve was to find whether these movements were harmful or useful to distinct vision. They might be blurring our vision, rather like the blurred photograph you get if the camera shakes during an exposure. Your eyes are shaking all the time when you are trying to see something clearly. Would you be able to see even better if this eye tremor could be stopped? Or are eye movements an essential part of our visual apparatus, so that without them our ability to see would be lessened?

The best way to decide between these two possibilities is to stop or stabilize the eye movements and see what happens to vision. We use a piece of apparatus which keeps the image of a target stationary on the retina whatever movements the eye might make. The subject wears the contact lens and mirror described earlier. A projector sends a beam of light on to the mirror carried by the contact lens and from there it is reflected through an optical system back into the subject's eye. If the eye rotates the reflected beam moves, but if the magnification of the optical components is arranged properly, the angle of movement of the beam can be made exactly the same as the movement of the eyeball. This means that the image formed on the retina stays on the same part of the retina, that is on the same set of receptors. We call an image formed in this way a "stabilized retinal image."

It is rather an upsetting experience when first you see a stabilized image in this way. Imagine a small bright spot of light in the center of your field of view; examine this spot of light carefully and when you have seen enough of it look away to some other place. The spot of light promptly jumps so that it is still in the center of your field of view. Whatever you do, you can't look away from it.

Now what happens to vision when the image is fixed on the retina in this way? The most spectacular change is a decrease in the ability of the eye to distinguish between regions of differing brightness. For example, we often use a target consisting of a circular field of light divided vertically, one half of this field being noticeably brighter than the other. In stabilized vision the bright half eats into the darker part of the field, the line of demarcation between the two halves seems to fade out and the whole field appears to be of uniform brightness. Quite large brightness differences disappear in this way and would appear as uniform patch of light. This sort of experiment establishes that brightness discrimination depends largely on the movements of the eye, because when we fix the image on the retina we can no longer discriminate between two areas of different brightness.

In order to find out why this is so, we must turn to the work of the electrophysiologists. These are the scientists who record the signals which flow in the nerves of animals when the sense organs are stimulated.

Their experiments indicate that steady illumination of a retinal receptor is not too effective in the generation of nerve impulses, but changes in illumination produce powerful bursts of nerve signals. We can apply this idea to help explain the results of our experiments with stabilized image. The retina consists of a mosaic of about a hundred million receptors. Each receptor is connected to the brain through the optic nerve fibers. When a pattern such as the half bright-half dim patch of light is first cast on to the retina, all the receptors receive a change of illumination. This will produce a high rate of impulses in all the nerves leading from the retina to the brain. The brain will interpret these signals, and will perceive a field which is bright on one side and dark on the other. If the image is stabilized on the retina, however, no further change of illumination will occur; the nervous impulses will die down and our perception of the field, and in particular of the brightness difference between the two halves of the field will be lost. But suppose that the image is not stabilized and eye movements do take place. The image is now in motion on the retina and some receptors will move from one side of the brightness boundary to the other and then back again. These particular receptors near the boundary will therefore be subjected to a continual change of illumination, from the bright to dark and back to bright again. They will be continually switched on, switched off, switched on, switched off and so on, and so all those receptors lying along the boundary will produce a high rate of impulses in the optic nerves connected to them. Receptors well away from the boundary receive no such change and therefore give rise to no signals in the optic nerve. So the brain receives a set of signals telling it where the boundary between the bright and the dark parts of the field lies. It is as though a photograph imaged on the retina is converted into a line drawing before it is signalled to the brain.

Now the brain is very good at filling in gaps in the visual field. We all have a blind spot in each eye, but normally they cause us no trouble since the brain fills in the part of the picture which is obscured by the blind spot. In the same way if the brain has enough information to show it where the boundaries lie between areas of different brightness, it can fill in the rest of those areas at the appropriate brightness levels and so build up a complete picture of the world around us.

# PROBLEMS IN TRACHOMA RESEARCH

**Phillips Thygeson, M.D.**

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Dr. Thygeson is ophthalmology professor and director of the Francis I. Proctor Foundation for Research in Ophthalmology which, among its other research activities, has been designated by the World Health Organization as an International Reference Centre for Trachoma. A recipient of numerous research awards, Dr. Thygeson is an editorial staff member of the *American Journal of Ophthalmology* and the *Survey of Ophthalmology.*

According to World Health (May 1965 issue), trachoma is still the "greatest single world cause of progressive loss of sight." World Health Organization estimates made 10 years ago gave a figure of 400 million sufferers from this disease. Present WHO estimates are still larger (500 million). This reflects (1) world population growth in this period, (2) the discovery of trachoma in populations not previously surveyed, and (3) the disappointing results of control programs, except in some European countries with high standards of living.

Although the causal agent of trachoma—a small, round elementary body 0.25 $\mu$ in diameter—was seen in conjunctival epithelial cells by Halberstaedter and Prowazek in 1907, cultivation of the agent was not achieved until 1957 when T'ang and associates grew it on the yolk sac of the developing egg. This led to a revival of laboratory research on trachoma, and at the present time there are laboratories all around the world that are engaged in some sort of research on the disease. At first considered a large virus, the causal agent of trachoma has been shown to have many properties of bacteria. It is now known to belong to a large group known as the PLT (*P*sittacosis, *L*ymphogranuloma, *T*rachoma) group with properties lying between those of the true viruses and those of the Rickettsia.

Trachoma is a chronic disease of the conjunctiva and cornea which causes visual and other disability by inducing scar formation in both structures. According to its extent and location, the corneal cicatrization may produce any degree of visual loss. To this the conjunctival scars may contribute by causing distortion of the lids with inturning of the eyelashes. These abrade the corneal surface and cause ulceration. When the conjunctival cicatrization is severe, it may close off the secretory ducts from the lacrimal gland and cause "dry eyes", or keratitis sicca. From this condition, corneal opacification and visual loss often result. By virtue of its chronicity, moreover, trachoma often picks up secondary bacterial infection. In such countries as Egypt, for example, superinfections with the gonococcus and Koch-Weeks bacillus may lead to much more severe corneal scarring than would have resulted from the trachoma alone.

The epidemiology of trachoma has received a great deal of attention. It is known that as a rule the disease spreads in the family as a result of close contact, as between mother or grandmother and child or among siblings of pre-school age. Spread is encouraged by poverty and poor hygiene, particularly in desert areas of the world where lack of running water in the homes makes normal cleansing procedures impossible. Flies and eye gnats are known to be vectors of various bacterial conjunctivitides, and most trachomatologists feel that although formal proof is still lacking, such vectors play an important mechanical role in the spread of trachoma also.

Until the introduction of the sulfonamides in 1938, no real progress had been made with the treatment of trachoma since the days of the Pharaohs. Surgical methods to relieve lid distortions had been developed, but there were no medications for the trachoma itself other than the cauterizing agents (copper salts) that had been used by the Egyptians many centuries before Christ (Ebers papyrus, 1800 B.C.). Fortunately for the world, trachoma has shown a remarkable tendency to disappear from populations whose standards of living have risen and among whom personal and family hygiene has improved. For example, trachoma was once widespread in northern Europe, particularly in France, Belgium, and Germany after the Napoleonic wars, but in the century that followed it diminished in this region in both frequency and severity until it was no longer an important cause of blindness. In such less fortunate areas as the Mediterranean basin, the Middle East, and the Orient, however, it continued unabated.

In 1938 Loe and others found that trachoma responded to orally administered sulfanilamide. Later on it was shown that the disease responded also to topically applied broad- and medium-spectrum antibiotics. Treatment by either method took a long time, however, and was not always effective. When the cured patient returned to an infected household, reinfection usually occurred. In spite of these shortcomings, the sulfonamides were used effectively in such countries as Austria and England to eliminate the trachoma problem almost entirely. But in the depressed areas of the world, where the disease affected a major portion of the population, none of the sulfonamide or antibiotic campaigns has materially reduced its prevalence. In the United States an expensive sulfonamide campaign against trachoma in our Indian population was temporarily successful, but among the tribes of the southwest, where water is scarce and family hygiene poor, the disease later returned in full force. At the present time trachoma is still a major problem in our southwestern Indian and Mexican population, and sporadic cases are still being seen in the white population.

Epidemiologic study of the sporadic cases in adults often fails to uncover any contact with known trachoma. To account for these cases, an attempt is currently under way to establish or rule out the genital tract as a source of the trachoma agent. It has of course long been known that the agents of the related diseases, inclusion conjunctivitis and lymphogranuloma venereum, infect both the genital tract and the eye. If a genital localization of the trachoma agent can be proven, it will of course change the present conception of the transmission of the disease.

It is now recognized that a great deal more research will have to be done before trachoma can be eradicated from depressed populations. It is true that individual cases can be treated effectively by present methods, and that if such patients are not returned to an infected household or surroundings, cure can be permanent. On the other hand, success is only temporary in such populations as our southwestern Indians. Among these tribes the school children are regularly treated and cured, only to return with reinfections after the summer vacation. Campaigns aimed at treating entire families are expensive, and particularly so when applied to nomadic populations like our Navajo Indians.

## Present Status of Trachoma Control

Present methods of diagnosis and therapy are adequate only for isolated cases of acute or subacute onset in which the clinical signs are clear-cut and for which controlled therapy under hospital or clinic conditions is attainable. Present methods are not adequate for the diagnosis of childhood trachoma of insidious onset, or for the treatment of primitive populations whose cooperation is difficult to obtain. Treatment of "captive" populations such as school children has only limited value since reinfection from parents, relatives, and preschool siblings is a common occurrence. Under mass conditions, as in North Africa, the Middle East, and some parts of Asia, present methods of trachoma control must be considered at best a holding operation. With our present techniques, eradication of the disease is possible only among people with high standards of living who are susceptible to health education and whose health authorities have sufficient funds to conduct trachoma control on a family basis.

It is obvious, therefore, that help must come from trachoma research if trachoma is to be eradicated, or reduced to a minimum, in parts of the world where it is now a serious problem. It is true that the disease could be expected to regress spontaneously if widespread, marked improvement in economic conditions and the general level of education, particularly health education, were to take place. It is clear, however, that in the most seriously affected areas of the world, such improvements will come slowly, and that worldwide relief from this crippling disease should not have to wait so long.

## Trachoma Research

The current trachoma research programs that can be hoped to contribute to trachoma control will be considered under the following headings: (1) laboratory diagnosis; (2) chemotherapy; (3) vaccination; (4) control of secondary bacterial and viral infection; (5) epidemiologic studies to uncover a means of breaking the reinfection cycle; and (6) health education.

*Laboratory diagnosis.* Clinical diagnosis can be made with reasonable certainty in established trachoma on the basis of the presence of tarsal follicles, conjunctival scars, or gross pannus; but clinical diagnosis in the early stages of the low-grade, often symptomless childhood disease poses a serious problem. Such cases are often confused with folliculosis, which is a benign lymphoid hypertrophy of the conjunctiva widespread among children, or with the various forms of chronic follicular conjunctivitis which ordinarily never develop pannus or scars or any visual complications whatsoever. In the hands of the skilled observer, the recognition of the so-called "micropannus" of trachoma by means of the biomicroscope has improved the clinical diagnosis of these early cases. In many instances, however, diagnosis must still be delayed until classical clinical signs are present.

Laboratory diagnosis by recognition of the Halberstaedter-Prowazek inclusion bodies in conjunctival epithelial cells has been useful in florid cases or cases with acute onset, but the inclusions are too few in number to be of much use in old chronic cases and in childhood cases of low activity. The method is not sensitive enough to have any value at all under field conditions. A somewhat more sensitive method of microscopic diagnosis became available when Rice demonstrated an iodine-staining glycogen matrix for the inclusion body. With this stain the contrast is such that the inclusions can be recognized under low magnification, but even this method is not of much use under field conditions.

When Roger Nichols and his coworkers from the Harvard School of Public Health adapted the immunofluorescence technique of Coons to the trachoma work, a great advance in microscopic diagnosis resulted. These workers were able to show that trachoma inclusions in very small numbers could be detected by specific fluorescence under the ultra-violet light microscope when conjunctival scrapings were stained with fluorescein that had been tagged with trachoma antibody. These results were soon confirmed by Lavelle Hanna at the University of California and by Hans Bernkopf of Hadassah University in Israel. The immunofluorescence method is now being tested by the University of California group on trachoma of Indian children of the southwest. The method is many times more sensitive than the old Giemsa method and represents a major diagnostic "breakthrough." It should aid not only in the detection of very early cases of the disease but in determining when cure has been obtained. It is now established that some cases that appear to be clinically cured are in fact subclinically active cases that harbor the trachoma agent and could spread the disease.

Other laboratory attempts at diagnosis, as for example by cultivating the agent on the yolk sac of the developing chick embryo, by demonstrating antibodies in the serum of patients, or by demonstrating specific skin reactions to intradermally injected antigen, have not yet been signally successful. In the hands of Collier and his coworkers at the Lister Institute in London, the culture method has been successful in as high as 50 per cent of cases, but it is tedious, costly, and often inconclusive so that no practical application of it is as yet in sight. Other laboratories have had a much lower success rate. A simpler and more sensitive culture method is greatly needed.

Serological tests have been even less rewarding. It has been possible to demonstrate complement-fixing antibodies in a small proportion of trachoma cases, but the test is nonspecific even when positive, since the C.F. antibodies are group antibodies and the test fails to differentiate psittacosis, trachoma, inclusion conjunctivitis, and lymphogranuloma venereum. No specific antibodies have yet been demonstrated in the sera of trachoma patients. Less rewarding still have been attempts to develop a specific skin test for trachoma like the Frei test for lymphogranuloma venereum.

*Chemotherapy.* No drugs more effective against trachoma than the sulfonamides (first used in trachoma in 1938) have yet been found. Attempts to use the sulfonamides locally have met with only limited success since the sulfonamide effect is viristatic rather than viricidal, and a steady therapeutic concentration must be maintained in order to obtain a cure. Since this can be done only by very frequent applications of the drugs, both day and night, it is impossible under ordinary field conditions. Use of the long-acting sulfonamides, which require only one dose a day, has been moderately successful. They carry a hazard, however, since it is difficult to eliminate the drug when a drug reaction occurs.

Nevertheless, in isolated cases and in cases that can be supervised by trained personnel, as may be the case in boarding schools, sulfonamides are the treatment of choice and give the highest percentage of cures. A serious handicap is that a minimum of two weeks of therapy is necessary, and experience has shown that primitive populations rarely tolerate such prolonged medication unless hospitalized. Unless a sulfonamide with viricidal properties can be developed, treatment time will of necessity be prolonged since the causal agent is eliminated only by the desquamation of epithelium. Attempts to speed up this desquamative process by the use of silver nitrate and other cauterizing agents have met with only limited success, but research along these lines is continuing at the University of California.

The action of the broad- and medium-spectrum antibiotics when used topically is no faster, but the antibiotics have several advantages over the sulfonamides, including safety. When a drug such as achromycin, suspended in oil, is used three or four times daily, a treatment time of four or more weeks is required to effect a cure. This regime is well adapted to school children but fails regularly in the treatment of adults and preschool children. The drug is irritating, causes temporary blurring of vision, and is soon abandoned by primitive peoples.

The intermittent treatment schedule that was developed by a World Health Organization team in Morocco has certain advantages. With this schedule the antibiotic is used for three or four consecutive days in every month for five months. This is better tolerated by the patients than continuous treatment and has the advantage of preventing or minimizing the common secondary bacterial infections.

In spite of active chemotherapeutic research, no drugs superior to the broad-spectrum antibiotics and the sulfonamides have been discovered. Such research is continuing in several laboratories, however, in the hope that new chemotherapeutic agents, alone or in combination, may shorten treatment time and in this way be more useful in mass campaigns.

*Vaccination.* Trachoma is a localized eye infection that often heals spontaneously, particularly in children, but which does not convey immunity. Trachomatologists feel certain that in children in endemic areas there is a process of infection, spontaneous healing, reinfection, and occasionally superinfection with the agent. It is known that some races and some individuals are resistant to trachoma infection, but total natural immunity does not seem to exist. The American Negro, for example, is remarkably free from trachoma in spite of the fact that economic conditions and conditions of personal hygiene have in the past been such that trachoma might have been expected to flourish among them. This immunity of the American Negro is only relative, however, as was recently shown in an accidental infection of a Negro animal caretaker at the University of California. The accidentally induced disease was mild but typical, and the agent of trachoma was isolated from it.

In spite of this lack of natural immunity and the frequent occurrence of reinfections, there is still a theoretical basis for vaccination trials. The agent of trachoma grows in the surface epithelium of the conjunctiva and cornea and has very little contact with the immunity-building tissues of the body. In vaccination a mass of antigenic material—in this case, cultivated trachoma agent—is injected subcutaneously or intramuscularly so that the antigenic stimulus is many times that of the natural disease. This antigenic stimulus can be measured in part by determining the amount of group complement-fixing antibody.

On the other hand, the microorganisms of the psittacosis-trachoma-lymphogranuloma venereum group are notoriously poor immunizers, and there is no example of successful vaccination against any of the numerous diseases produced by its members. However, some modification of the disease has been obtained in the case of turkey ornithosis, a serious disease in the turkey flocks of the west coast. This modification of the turkey disease is reflected in a lower mortality and a milder course.

At the moment five major institutions (Harvard School of Public Health, Lister Institute of Experimental Medicine, University of Washington School of Medicine, The South African Institute for Medical Research, and the Instituto Superiore de Sanita of Rome) are engaged in human vaccine research. The results of these researches were summarized at a meeting sponsored by the WHO in Geneva in August of this year. None of these laboratories reported striking success, but all reported that the attack rate of trachoma could be influenced by vaccination. This influence consisted for the most part in delaying the age of onset of trachoma in the vaccinated children. For example, the University of Washington group (headed by Dr. J. Thomas Grayston), in reporting their vaccination studies in Taiwan, claimed that the vaccine was 60 per cent effective in preventing trachoma at the end of one year, but this figure had dropped to 10 per cent at the end of five years. The Harvard group reported that the vaccination of infants in Saudi Arabia was effective in minimizing trachoma infection for a period of six months, but that this effect had disappeared completely at the end of two years whether or not booster doses were given. The South African group (headed by Dr. Graham Scott) noted that over a 20-month period the attack rate in 100 control children was considerably less than in a non-vaccinated group of 100 children.

The vaccination studies are complicated by the fact that more than one immunologic type of trachoma agent is usually found in one community so that the vaccine must be polyvalent, and by the fact that live vaccine which would be more effective, must be avoided because of the possibility that tissues other than those of the eye may be susceptible to infection with the agent.

Another serious theoretical complication of vaccine therapy has arisen. It has been shown in monkeys that incomplete vaccination sometimes induces allergic manifestations in the cornea and conjunctiva that markedly increase the severity of the disease. In studies of volunteers infected with the benign related disease known as inclusion conjunctivitis, the University of California investigators have encountered these allergic phenomena after reinfections with the inclusion conjunctivitis agents. Inclusion conjunctivitis is a disease ordinarily without corneal complications, but second and subsequent attacks are frequently associated with superficial corneal opacities which are believed to result from a combination of antibody and antigen in the cornea which may temporarily reduce vision.

It is of interest in this connection that one theory which attempts to explain the great variation in the severity of trachoma suggests that severity is associated with the development of hypersensitivity. Hypersensitivity is ordinarily minimal or absent because of the localized nature of the eye disease. This unexpected complication of immunity raises a serious problem for vaccinators.

At the present moment vaccination holds little promise of conferring complete protection from the disease, but it does hold some promise of conferring a relative immunity which could minimize the reinfection and superinfection problem that is so important in trachoma-endemic areas. For example, if the reinfection of treated school children could be prevented by vaccination, the whole picture of trachoma in our southwestern Indians would be modified, and an expensive and difficult family treatment program could be avoided. A combined treatment-vaccination program is therefore a distinct possibility for the future.

The WHO group concluded that continued vaccine research was very much in order in the hope of obtaining ultimately a widely applicable vaccine. It is known that some strains are more antigenic than others, and it is hoped that fractionation of antigens may yield fractions which will be highly antigenic without being toxic.

*Control of secondary bacterial infection.* The importance of secondary bacterial infection varies greatly throughout the world but is greatest in desert and tropical areas where spring and fall epidemics of Koch-Weeks conjunctivitis add greatly to the severity of trachoma. Other bacteria, including Moraxella and staphylococci, can superinfect trachoma, and in certain parts of the Middle East there is a much dreaded superinfection with gonococci which are highly pathogenic for the cornea and account for much blindness through the production of ulceration followed by dense scarring. Present methods of chemotherapy, although not very effective in controlling trachoma, have been remarkably useful in the control of secondary infections. Particularly valuable has been the WHO's intermittent schedule of treatment with achromycin, used in ointment or oil in countries such as Morocco where Koch-Weeks conjunctivitis is devastating. The widespread use of this method in Morocco, for example, probably accounts for the greatly diminished visual loss there, in spite of the fact that trachoma itself has not been greatly modified. Certainly this method of control should be extended to all parts of the world where epidemic bacterial conjunctivitis is a problem. Indeed, the control of bacterial infections is the only really bright spot in the overall trachoma picture.

*Epidemiologic studies.* Recent epidemiologic studies by Foster of a Pima Indian village are of interest in showing the family nature of trachoma, and in showing that the peak of trachoma infection takes place before the age of 8 years. Foster pointed out that while maternal infection is important, transmission from child to child in playing, wrestling, and sleeping together is also important. It has long been known that in the absence of running water, the family wash basin and the common towel are potent forces in intrafamilial spread. Studies are now under way among the southwestern Indians to determine the effect of the introduction of running water into a village. Presumably the chain of transmission at the wash basin will be broken, and improvement in personal hygiene in the family will be reflected in a lower transmission rate.

Another attempt at interrupting the infection cycle is being undertaken by Division of Indian Health officers in the Indian area. More than 50 per cent of deliveries are now being accomplished in Indian hospitals. This gives an opportunity to diagnose and treat the maternal disease under hospital and out-patient conditions. It is felt that an adequate campaign to treat all maternity cases will result in a considerable modification of the childhood attack rate.

*Health education.* Health education in primitive populations has in general been disappointing. There is little or no evidence that health education campaigns by means of posters, film strips, lectures, etc., have had any influence on trachoma. Efforts at health education among our southwestern Indians have been under way for many years. An excellent film by Dr. Fred Loe for use in the Navajo area was made in 1940 and is still being used. It emphasizes the role of the wash basin and towel in trachoma transmission and offers a means of minimizing this hazard. Its effect on the Indian population has not been significant. However, a steady improvement in the economic and educational status of the Indians is under way, and health education should gradually become more effective. If simple household hygienic measures could be taught, the spread of trachoma could be prevented. Further research along these lines is therefore greatly needed.

### Investigations on Inclusion Conjunctivitis and Oculogenital Disease

The benign, self-limited disease known variously as inclusion conjunctivitis, inclusion blennorrhea, or paratrachoma, has long intrigued trachoma investigators because of its many similarities at onset to trachoma, and because of its epidemiologic relationship to a benign cervicitis of the female and a nongonorrheal urethritis of the male. An old concept that inclusion conjunctivitis may be a simple variant of trachoma has been revived in recent years by Barrie Jones of London. Jones has claimed the production of a typical trachoma, with pannus and scars, in a human volunteer with an isolate from inclusion conjunctivitis. Our University of California group, on the other hand, has been able to produce only typical benign self-limited inclusion conjunctivitis with two strains isolated from inclusion conjunctivitis.

In any event, Jones' concept has stimulated much work on the subject of oculogenital disease, both in the United States and abroad. At the University of California we have isolated one strain of PLT agent from the urethra of a trachoma case, and have studied over 30 cases of inclusion conjunctivitis with urethritis or cervicitis. It is evident that genitourinary disease caused by members of the PLT group of agents is widespread, and that an additional type of venereal disease, now known as "inclusion urethritis" and "inclusion cervicitis" must be added to the already long list of such diseases.

Much research is still needed to determine whether or not tissues other than the urethra and cervix may be involved, and whether or not scars and strictures may result. PLT agents isolated from genitourinary infections must be tested on simian hosts, and their relation to trachoma, inclusion conjunctivitis, and lymphogranuloma venereum determined.

### Summary

Trachoma is still the eye disease of greatest worldwide importance. It is one of the two epidemic eye diseases that have received major attention from the WHO. The disease is unusual in having a world organization—the International Organization Against Trachoma—devoted to it, and in having its own special journal—the International Review of Trachoma. Trachoma was the subject of an international meeting of ophthalmologists and virologists that was sponsored by the New York Academy of Sciences in 1962. A second international meeting devoted to the disease is to be held in San Francisco in August, 1966.

The Francis I. Proctor Foundation of the University of California San Francisco Medical Center has been designated by the WHO as an International Reference Centre for Trachoma. The Centre will collect and categorize strains of the agent from all parts of the world, will serve as a training center for investigators of the disease, and will collect and make available to all interested parties the results of investigations in laboratories throughout the world.

A major breakthrough in trachoma control will occur when new and more rapidly acting chemotherapeutic agents are developed, or when an effective vaccine can be evolved, or when world economic conditions improve sufficiently to permit health education measures and simple epidemiologic control measures to be effective.

It is of interest that major trachoma studies are being conducted in all parts of the world, and particularly in such countries as the United States and Great Britain where trachoma itself is not a major problem.

# UVEITIS

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The peak incidence of this condition occurs in children below the age of 13, and again during the highest earning years of 30 to 50 years of age. Thus, this condition is of considerable socio-economic importance, not only because it produces blindness but also because it incapacitates other individuals for prolonged periods during their most active years.

## Types of Uveitis

### A. *Acute, non-granulomatous iridocyclitis*

"Uveitis" was referred to above as a group of diseases because there are several distinctly different types of ocular inflammation. The first of these may be referred to as acute, non-granulomatous "uveitis." This usually affects the anterior portion of the eye, producing marked redness of the globe, light sensitivity, and blurred vision. The typical attack, if untreated, lasts from two to three weeks and then clears, leaving very little residual damage to the globe. However, recurrence is the rule and, after a number of exacerbations, the patients frequently develop cataracts and secondary glaucoma. This type of inflammation is often associated with rheumatoid arthritis of the peripheral joints and ankylosing spondylitis (poker spine).

An excellent experimental model of this type of ocular inflammation can be produced in rabbits and guinea pigs. Because of the frequent association of acute, non-granulomatous iridocyclitis and arthritis in the same person, it is hoped that any clues found from the study of the experimentally produced "uveitis" in animals will shed light on the cause of arthritis—and vice versa, that any advances in arthritis will aid in the treatment of this form of "uveitis."

### B. *Auto-immunity*

Some of the most intriguing afflictions of man are thought to be due to auto-immunity. In such diseases the patient is thought to become allergic to his own tissues. Some examples of this are: demyelinizing diseases such as multiple sclerosis; thyroiditis; sterility in the male; and some forms of kidney disease. It is interesting that Uhlenhuth in 1909 first used the lens of the eye to demonstrate that an animal could be sensitized to its own tissues. It is now thought that one form of uveal inflammation in man results from a sensitization to his own lens. Another possible type of auto-sensitivity is sympathetic ophthalmia. This is a most dreaded eye disease, for it results in destruction of a normal, uninjured eye following injury and inflammation of the opposite eye. It is obvious that further understanding of these types of ocular inflammation would lead to advances in the poorly-understood systemic auto-immune diseases listed above.

### C. *Uveitis from specific organisms*

It has long been known that patients infected with certain systemic types of infection also frequently develop "uveitis." The best known examples of this are leprosy, onchocerciasis (a microfilarial disease that occurs in Africa), and leptospirosis (a spirochaetal infection that is prevalent in the Eastern European and Asian countries). In this country, in the past, syphilis and tuberculosis were thought to be frequent causes of uveal inflammation; and ocular involvement is still a common complication of sarcoidosis.

### D. *Toxocara canis*

Recently, Forrester and Zimmerman, in this country, and Ashton, in England, have made notable contributions to the study of a rare but interesting type of ocular inflammation that occurs in children. This is caused by the dog roundworm, Toxocara canis. It results from children playing with puppies, and frequently from children eating dirt in which the ova had been deposited.

### E. *Toxoplasmosis*

One of the best documented and most thoroughly studied forms of "uveitis" in this country is that which is due to the parasite Toxoplasma gondii. About 25% of the adult population in this country are thought to be infected with this organism. In most instances the disease is totally asymptomatic. In relatively rare cases, it produces symptoms of chills and fever, enlargement of the lymph nodes, pneumonitis, myocarditis, and encephalitis. When transmitted from a pregnant mother to the fetus, it produces stillbirths, mental deficiency, and blindness. The principal ocular lesion, both in children and in adults, is an inflammation deep in the eye (i.e., in the retina and choroid) that produces no external evidence of inflammation, but a marked loss of visual acuity. Treatment of the ocular inflammation is rather unsatisfactory. The principal students of this form of uveal inflammation are Forrester, Hogan, Sabin, Jacobs, and Frenkel.

### F. *Histoplasmosis*

The last type of ocular inflammation to be described has been of particular interest to those of us working in the Wilmer Institute. This is a lesion that occurs primarily in young persons between their 20's and 50's, and results from a bilateral loss of vision due to a hemorrhage in the macular area, or visual center of the retina. Thus, it frequently causes legal blindness. A specific organism has not been isolated from the eyes that have become available for study, but a high percent (94%) of patients with this specific type of ocular lesion have a positive skin test to the fungus, histoplasma capsulatum.

There are many other types of uveal inflammation for which no specific cause has been found. A principal reason for this is that the eyes cannot be biopsied during the active stage of inflammation because this might result in a loss of the globe, or might produce sympathetic ophthalmia with a loss of the second eye. Nor do these eyes require enucleation (removal) during their acute inflammation, for it is always hoped that the disease can be quieted and vision saved. Thus, only when the eyes become blind, shrunken, and painful, and the inflammatory process is "burned out" (no longer specific), that the eyes become available for histological and microbiological investigation.

*The science writers could do a great service by pointing out the lack of the available material for study and by requesting their readers to sign up with the Eye Bank, particularly if they have ocular disease.*

One of the major problems in ophthalmology is a group of diseases that have been called "uveitis." These consist of a non-purulent inflammation of the vitreous, retina, and uveal tract (iris, ciliary body, and choroid).

The exact incidence of this disease is not known because the condition is thought not to be transmitted from one person to another (as is smallpox, diphtheria, etc.) and is therefore not required to be reported to the Public Health Service. A recent study in Rochester, Minnesota by Darrell, Wagener, and Kurland has indicated, however, that the prevalence of this condition is about 204 cases per 100,000 people, or 0.2%.* This is in close agreement with a house-to-house survey made by Feldman and Mou in Syracuse, New York.

It is thought that about 5% of these persons go blind. The exact prevalence of blindness due to "uveitis" is also not known because of the difficulty in reporting; however, various surveys have estimated that from 10% to 20% of all blind persons have lost their vision because of "uveitis."

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**Epidemiology of uveitis*—Darrell, R. W.; Wagener, H. P.; and Kurland, L. T., Arch. Ophth., Vol. 68, October 1962, pp. 502-514.

# CANCEROUS AND PSEUDO-CANCEROUS LESIONS IN AND ABOUT THE EYE

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## Summary

Our clinicopathologic and follow-up studies during the past several years have led us to the conclusion that many of the tumors occurring in or about the eye are not nearly so malignant as was formerly thought. While some of these lesions must still be considered "low-grade cancers", others are completely benign growths. Examples are found in the skin of the lids, on the outer surface of the eyeball, in various tissues inside the eye, and in the orbital tissues behind the eyeball. In contrast with these "low-grade cancers" and "pseudocancers", there is a smaller group of highly malignant cancers that may appear disconcertingly benign to both the clinician and the pathologist. A high index of suspicion coupled with experience permits early diagnosis and vigorous treatment; without this, a fatal course may be anticipated.

## Significance

A continuous reappraisal of our knowledge of the biologic nature of various tumors has very obvious clinical implications. On the one hand there is a group of tumors that we are learning to manage much more conservatively than was thought possible in the past, while on the other hand we are most anxious to be able to spot those that do really require early, radical, life saving treatment. The first group is particularly important in ophthalmology—partly because of their relative frequency, but mostly because the ocular tissues cannot be excised widely without creating very serious functional and cosmetic disturbances. A "small" tumor measuring only one-half inch in diameter occurring on the skin of the abdomen presents no diagnostic or therapeutic problem because it easily can be excised with a safe wide margin of normal skin about it. The same lesion occurring on the eyelid, on the eyeball, or inside the eye presents a very serious problem. Here, the ophthalmologist must think in terms of preserving normal tissue and normal function. He cannot afford to sacrifice a wide margin of normal tissue unless he is certain that it is necessary. If he is sure that this must be done to fight a lethal cancer, he is prepared to do so, but if the chances are great that the lesion is not truly cancerous, he will want to tackle the problem much more conservatively.

The same situation prevails with respect to radiation therapy. There are lesions in and about the eye that can be handled very satisfactorily by x-ray, radium, radon, etc. but again, these ionizing radiations are not without potential danger to various ocular tissues. Certainly, one would not choose to use large doses of ionizing radiation in the management of a non-cancerous ocular tumor.

## Background

In 1921 through the joint efforts of several American ophthalmologic organizations and the Army Medical Museum (the parent organization — established during the Civil War — of our present Armed Forces Institute of Pathology), there was established in Washington a Registry of Ophthalmic Pathology. The first fruit of this Registry was Major George R. Callender's study of 111 eyes removed for malignant melanomas (cancerous tumors that tend to produce a black pigment). He was able to show that not all of these melanotic neoplasms were equally lethal. Moreover, he could predict their biological behavior from their microscopic appearance! His observations were so accurate and helpful that today—almost 35 years later—we are still using his classification of this particular group of tumors.

Since then many other studies of the same sort have been undertaken by the Registry's staff to evaluate a broad spectrum of cancerous and pseudocancerous lesions of the eye, eyelids, and orbit.

## Techniques

Our techniques are really quite simple but they require perseverance and a cooperative effort on the part of the nation's physicians, mainly ophthalmologists and pathologists, and the patients and their families. The first step is to obtain a good description of the appearance and development of the lesion. (Oddly, we have learned that the history of the sudden appearance of a new growth and its very rapid enlargement usually signifies a benign reactive proliferation—not a cancerous lesion!) The second step is to prepare thin, well-stained sections of the excised tissues for careful microscopic examination. This permits grouping together lesions that have a similar microscopic appearance. The third step is to keep contact with the patient and his physicians to determine the subsequent course of events, taking into consideration all known factors that might influence the biologic behavior (natural life history) of a lesion (e.g., the extent of surgical intervention, use of radiation therapy, chemotherapy, etc.).

Frequently this type of follow-up study must be pursued for very long periods before the full picture emerges. For example, returning again to the intraocular melanomas, we have learned that following removal of an eye containing one of these cancers, a patient may remain in excellent general health for 20 years or longer and still die as a result of spread to other parts of the body (especially the liver). Many of the lethal tumors take 5 to 10 years to kill the patient. Thus, for these melanotic tumors we no longer speak of "5-year cures" but rather of "5-year survivals". By contrast there are other ocular tumors such as the retinoblastoma and the embryonal rhabdomyosarcoma (both of these incidentally are virtually never encountered in adults) that, when they prove lethal, almost always do so within the first 3 years after treatment. For these, then, "5-year survival" almost always signifies a cure.

I would like to cite two other examples of the importance of long-term follow-up study of cancer patients, both coming from experience with the successful treatment of retinoblastoma. Not too many years ago this tumor was almost 100% fatal. Today, if recognized early and treated properly it is almost 100% non-fatal. In the course of developing the present-day successful treatment, there was a period when intensive x-ray therapy was used. This was successful in destroying the tumor but in doing so it also destroyed the eye. To make matters even worse, the intensive ionizing radiations sometimes induced changes in the tissues about the eye that subsequently led to the development of new, entirely different cancers that proved to be lethal. The point that I wish to make here is that this new cancer often took 5 to 15 years to appear. Without systematic long-term follow-up, correlating the course of events with therapy, the cause-and-effect relationship of this excessively high dose of x-ray and the subsequent appearance of a new cancer would not have been appreciated.

The second example that I wish to cite concerns the fate of retinoblastoma-survivors when they later in life have children of their own. It is now quite clear that many survivors pass on the retinoblastoma trait to their offspring, apparently due to the fact that a permanent genetic transformation has occurred in their cells. Every retinoblastoma survivor must therefore be warned of this possibility. In such cases, his offspring should be given the benefit of a very careful eye examination at birth and periodically throughout the first few years of life. Recently in Washington, we saw the results of such a situation. A mother who was a retinoblastoma survivor and who had already had one child with retinoblastoma, gave birth to an apparently normal baby. Careful ophthalmoscopic examination when the baby was just a week old revealed a small retinoblastoma. Such early detection offers the best chances for control of the tumor.

Let me add a few words about the importance of obtaining eyes postmortem for histopathologic study. It is an interesting fact that we know the least about many of the most prevalent diseases that impair vision without causing complete blindness. Every eye that is removed in a hospital operating room is studied histopathologically as a routine procedure. These eyes, however, generally reveal only the end stages of such diseases as glaucoma, uveitis, diabetes, myopia, etc. It is much more important for the pathologist to study tissues removed during the very early stages if he is to obtain clues as to cause. Rarely does the pathologist have the opportunity to study the early phases of most diseases because such eyes are not removed either surgically or postmortem. The laws in most states require special permission to remove the eyes postmortem—the routine permission for a "complete autopsy" does not legally authorize the pathologist to remove the eyes at the time of autopsy. If people were educated to appreciate the importance of obtaining eyes postmortem—not only for eye bank purposes, but also for histopathologic study and correlation of tissue changes in the eyes with those in other viscera—I am sure that most families would be cooperative. I suspect that particularly in the case of patients who have had an eye disease that might be genetically determined (hereditary) – e.g. glaucoma, myopia, retinitis pigmentosa, corneal dystrophy, optic atrophy, etc. – we would find enthusiastic cooperation.

# CHROMOSOME ABNORMALITIES IN RETINOBLASTOMA

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Dr. Lyons is assistant professor of anatomy and experimental medicine at the University of Oregon Medical School. His continuing work in cytogenetics, especially retinoblastoma and familial patterns of aneuploidies and mosaicism, is among major research projects under his direction.

## Summary

We have found an abnormal chromosome in cells from a patient with retinoblastoma, a malignant tumor of the eye. A chromosome of the D group (one of seven groupings based on size and shape) is missing and is replaced by a much smaller fragment which is probably the remnant remaining after breakage or deletion of the original D chromosome. A similar finding has been reported by Drs. K. P. Lele, L. S. Penrose and H. B. Stallard of the Galton Laboratory in London in one of six patients with retinoblastoma. Recognition in only two of more than 25 patients so studied suggests that this change at the chromosome level may not be present in all patients with this disease, or, if present in a lesser degree, may not be recognized with techniques now used.

Because this tumor is known to be inherited in some families, the patient's parents, maternal aunt and maternal grandmother were also examined. No other family member was known to have retinoblastoma. The mother, maternal aunt and maternal grandmother all had some cells which are aneuploid, i.e. contain more or less than the normal number of chromosomes. A few of the mother's cells contained the same deleted D chromosome present in all of her son's cells and both she and her son showed frequent broken chromosomes.

## Significance

Chromosome studies were done on the patient before he had a diagnosed tumor because he had been born with numerous congenital anomalies including microphthalmia (small eyes) and colobomata (a keyhole shaped defect in the iris). Another kind of chromosome abnormality, the presence of one too many D chromosomes, usually shows similar abnormal development of the eyes. These observations could mean that genes carried on one of the D chromosomes have to do with normal development of the eyes.

From our studies we feel that the family described may possess an inherited trait that results in errors of cell division and easily broken chromosomes. The abnormal D chromosome presumably arose from such an error and is present in all of the cells of the patient; his mother has this abnormal chromosome in only a few of her cells and therefore developed normally.

The relationship of the deleted chromosome to retinoblastoma is speculative but intriguing. A considerable genetic change or mutation can occur without visibly affecting the chromosomes simply because of the small size of the genes. A change in the number or type of genes controlling normal eye development might result in a disease such as retinoblastoma. The two patients with retinoblastoma, Dr. Lele's and ours, may be representative of another human malignancy associated with loss or deletion of normal chromosomal material. Similar findings (i.e. familial transmission of abnormal chromosomes) have also been reported for chronic granulocytic and chronic lymphocytic leukemia.

Families in which multiple members are affected by more than one type of cancer are well known. Genetic susceptibility to errors in cell division of the sort observed in this family may be one mechanism which predisposes to cancer.

## Background

Retinoblastoma is a malignant tumor of the retina which generally occurs in early childhood but occasionally occurs in adults (there is a recent report of the disease in a 53 year old man). Dr. A. B. Reese of Columbia University in New York, in his text of eye tumors, notes an incidence of about 1 in 23,000 live births, which would make this a relatively rare tumor.

The untreated tumor eventually brings about a protrusion of the globe of the eye with a most pitiful as well as inescapable appearance. Because it is so obvious in advanced stages, the disease (or closely related phenomena) has been referred to in historical accounts for centuries. In his excellent recent account (1964) of the disease, Dr. E. B. Dunphy of Boston attributes the first clinical notation of retinoblastoma to an anatomist (Petrus Pawius) in the year 1597. The disease, however, was seldom referred to until a complete and prophetic description by a surgeon, Hayes, in 1767, in which he commented on many of the important features and behavior of the tumor as well as describing one of the most important physical signs leading to its diagnosis (a white rather than red light reflection from the retina). There followed a rather eventful as well as long history of retinoblastoma.

Though the tumor is quite malignant and outwardly disfiguring, it is peculiar that it occasionally does not send out massive metastases to the brain and other parts of the body with the result that the patient often lives a long time after the onset of symptoms. Enlargement of the untreated tumor usually creates considerable pain with seizures being common and the patient is generally very thin and wasted at the time of death. This grim picture has shifted remarkably with new methods of early diagnosis and treatment. Presently, the earlier cases can be treated by combinations of x-ray and drug therapy which result in cure rates as high as 90% even without destroying significant vision in the affected eye. Much of the pioneer therapeutic work done in this country has been accomplished by Dr. Reese and his colleagues over the past twenty years. One can say that the retinoblastoma patient has improved immensely.

It is generally believed that there are two forms of retinoblastoma, one occurring in a patient with similarly affected relatives (hereditary form) and the other arising as a spontaneous disorder without pre-existing retinoblastomas in the family (spontaneous or "mutant" form). In general, a given couple considering their chances of having a child with retinoblastoma would feel secure in knowing that only 1 out of, say, every 23,000 live children born may develop the disease (usually before the age of 10). However, if one of them has a family history of the disease and is, indeed, a *carrier* of the abnormality, then their chances of having an affected child will increase to 1 out of every 2 to 1 of 10 of their children. The reason for the variable frequency is caused by an unpredictable penetrance (relative strength or likelihood of expression) of the trait. It should be emphasized, however, that one-half of the children would inherit the trait(s) for the disease regardless of the degree of penetrance. Therefore, parents with a history of the disease in their family would worry about transmitting the disorder to their children. It would be of considerable value to be able to recognize the "carrier" of retinoblastoma and thus inform a prospective parent. Except for the possible use of chromosomes in the case we are reporting here, no such carrier detection is presently available.

### Techniques

Chromosomes from colchicine arrested metaphases (cells in division) of cultured white blood cells or skin may be photographed, counted, enlarged and then each chromosome can be cut out and arranged on a piece of paper. Such preparations from normal people contain cells with 46 chromosomes and these can be placed into one of seven fairly distinct groups based on their size and shape (Groups A, B, C, D, E, F and G). Abnormal number or structure can then be seen more clearly. Our attention was immediately drawn to members of the D group which contains six chromosomes (3 pairs).

### Human Interest

The patient was 12 months old when we began our studies and was the first and only pregnancy of a 19 year old mother and a 20 year old father. Both parents were enrolled in college at the time but withdrew from school after delivery of the patient because the severity of his anomalies demanded much time and money. The father had to take a full-time job to afford the numerous medical and non-medical expenses associated with a severely handicapped child. Eventually, care of the patient became somewhat routine and less expensive so that the father could return to school, but the mother has not been able to return. Both the mother and the father have resolved to have no more children of their own after living through this very unpleasant experience; they are now in the process of adopting a child because they do desire to raise children.

# CONTACT LENSES

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In spite of the fact that contact lenses were described over a hundred years ago, they have not been truly successful until the past ten years. Interest by ophthalmologists in contact lenses has waxed and waned, but after a number of false starts contact lenses appear to be "here to stay".

There are three main types of contact lenses now in use. In addition to these some new materials and new designs will be discussed.

### Corneal Contact Lenses

The corneal contact lens or a lens which has a diameter smaller than the diameter of the cornea was first described by Kevin Tuohy in 1948. While the idea was excellent and one which has proven enormously successful, the original designs and manufacture of the lens were so poor its use was greatly restricted. From 1948 through 1955 the corneal lens went through an evolution consisting mainly of reduction in the diameter of the lens, the thickness of the lens, and the design of the posterior curve in relation to the cornea to which it was to be fitted.

The present corneal lens is custom designed for an individual cornea. The diameter of the lens is dictated by the size of the apical or optical zone of the cornea. This apical zone can vary tremendously from one individual to another. (From 3.8 mm in diameter to 9.0 mm in diameter in over a thousand cases.) It may also vary from one eye to the other. (From 0.2 mm to 3.0 mm in 531 patients.) To determine the diameter of the corneal lens the longest diameter of the apical zone of the cornea is measured and to this measurement two millimeters is added for overhang, peripheral modifications and edge design—this technique is known as LD+2.

The central posterior curve of the lens is always designed slightly steeper than the flattest meridian of the cornea so that there will be clearance of the apex of the cornea.

The power of the lens, determined from the patient's refraction, is ground on the anterior surface of the lens.

The thickness of the lens is determined by the diameter and the power, but is the minimum thickness which allows for stability.

Such custom designed corneal lenses have proven to be successful in 90-95% of cases fitted, are tolerated all of the patient's waking hours, require additional modification in only about 50% of cases, and cause no damage to the eye.

The corneal lens is by far the most popular type of contact lens in the world. It is estimated that some nine to ten million people are wearing corneal lenses at the present time in the United States. There are some dangers which have only recently been publicized. They may be listed as follows: (1) A poorly designed or fitted lens may be tolerated by some patients even though the lens is causing damage to the cornea. There is good evidence that the cornea becomes less sensitive after wearing a contact lens or the patient may tolerate a poorly designed lens because of high motivation. (2) Some patients are foolish in the handling of the lens—improperly cleaning the lens or wearing the lens during sleep, etc. (3) Patients with corneal contact lenses have been known to develop corneal ulcers. There have been reports of eyes lost from these ulcers. It is not yet known whether corneal lens patients are more prone to corneal ulceration than patients not wearing lenses. No scientific investigation has been performed on this aspect.

### Scleral Lenses

The scleral lens is the oldest design of contact lenses, being originally blown from glass by F. A. Muller in 1887. The first real success with scleral lenses came with the molding of methylmethacrylate, first utilized by Orbig in 1938. A mold of the eye was taken and reproduced in plastic. The section over the cornea was hollowed out and an optical surface ground onto this portion. The chamber created between the back surface of the contact lens and the cornea was filled with a buffered salt solution. Since there was no circulation of tears the patient could tolerate this lens for only three or four hours at a time. Often the cornea became edematous within an hour or two. The design of this lens has remained essentially the same over the years, except with the experiences of Orbig, Norman Bier and Frederick Ridley, the lens has been fenestrated or channeled to allow circulation of tears beneath the lens.

While the scleral haptic lens does not give as good a wearing time as the corneal lens it can be used in certain conditions where a corneal lens is not applicable.

### Flush Fitting Scleral Lenses

One of the most exciting developments in contact lenses and even in ophthalmology, has been the development of the flush fitting scleral contact lens for the treatment of certain corneal diseases. The lens is used, not for visual purposes, but as an aid to healing. A mold is taken of the diseased cornea. This mold is duplicated exactly in the methylmethacrylate. Because of the perfect contour fit only a capillary layer of tears exists between the lens and the cornea, and the tears circulate freely. This lens has been found to be of great use in such conditions as chemical burns of the cornea, chronic corneal ulceration, neuroparalytic keratitis, bullous keratitis, lagophthalmos keratitis, exposure keratitis, pemphigus, Steven's-Johnson disease, mustard gas keratitis, in certain corneal dystrophies, in stromal herpetic keratitis, after corneal transplants, and in filamentous keratitis.

In some of these conditions flush fitting scleral lenses have proven to be the treatment of choice and after the cornea has healed vision has returned.

It is not known exactly how a flush fitting lens produces a therapeutic effect. It is the feeling of this author that it occurs in three ways: (1) The lens, worn twenty-four hours a day, protects the cornea from movements of the overlying lids. (2) The exact, contour fit of the lens produces a capillary layer of tears between the lens and the cornea with free exchange in the circulation. If there is a discrepancy between the back surface of the contact lens and the anterior surface of the cornea, tears tend to pool and to stagnate and can produce more damage, rather than healing. (3) The constant presence of the lens increases the temperature of the cornea by preventing evaporation of the tears and allows the cornea to operate at a higher temperature and great metabolism. The use of a thermophere, of fever therapy, or diathermy or wet heat has been known to be beneficial for years.

The use of a flush fitting scleral lens has replaced the use of a conjunctival flap in most of the conditions previously described. It has the advantage over the conjunctival flap in that: (1) It is possible to remove the contact lens and examine the cornea. (2) It is possible to remove the lens and take the tension. (3) It is possible to carefully follow the healing of the cornea beneath the lens. (4) Even though the cornea may never be able to support itself without the presence of the lens, some degree of correction can be obtained by grinding an optic on the anterior surface of the lens. Vision as much as 20/30 or 20/40 is possible even without an optical surface on the back of the contact lens. (5) It is possible to get good concentrations of medications to the cornea instilled into the conjunctival sac. (6) Corneas can perforate under a conjunctival flap.

### New Material for Contact Lenses

A couple of years ago two scientists in Prague, Czechoslovakia, Professor O. Wichterle and Dr. A. Dreifus, introduced a hydrophilic plastic for use in contact lenses. This plastic takes up its weight in water by 60%. The lens is hard when dehydrated but becomes soft as it takes up water. There are, however, a great many problems that must be overcome before this matter will be practical, such as the impregnation with bacteria and the problems with optics. The idea that a soft plastic lens can be used in the eye is intriguing. Professor Wichterle is continuing his research along these lines.

### Summary

While the greatest number of contact lenses being worn are purely for cosmetic reasons, they have also been found to be of therapeutic benefit in certain conditions of the cornea. One of the great advances has come from the interest in contact lenses by academic institutions now teaching the subject as part of their curriculum. Baylor was the first such institution. It was also the first institution to teach courses for ophthalmologists and technicians in contact lenses.

There are many problems that still must be solved before the ideal lens will be found. This will come inevitably from the cooperation of the clinician, academician, and basic scientist.

# THE FTA-ABS TEST—A NEW TEST FOR SERONEGATIVE OCULAR AND NEUROSYPHILIS

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Discussions of advances in neuro-ophthalmology today may include four of the following major aspects which may be considered as the 4 S's of neuro-ophthalmology. These are 1) Strokes, 2) Surgery, 3) Systemic, and 4) Syphilis. The progress being made in these areas of medical research may be covered in the following terms:

I. *Strokes*
  1. Advances in *diagnosis* of cerebrovascular disease (ophthalmodynamometry, carotid compression, posture, bright plaques of Hollenhorst and the like).
  2. Advances in *treatment* of cerebrovascular disease (carotid thromboendarterectomy, anticoagulation, and the like).

II. *Surgery*
  1. stereotactic surgery
  2. cryosurgery
  3. pituitary ablation
  4. nystagmus surgery
  5. hypothermia
  6. blepharospasm surgery

III. *Systemic*
The mnemonic for remembering this is the word *GEMS* – this stands for
*Genetics*
*Enzymology*
*Metabolism*
*Studies*
Thus, amino acidurias, histochemistry, neurochemistry, electron microscopy, and the like are making tremendous diagnostic advances, particularly in pediatric neuro-ophthalmology.

IV. *Syphilis*
This may be summarized as follows: "A negative blood test does NOT rule out syphilis". Emphasis will be placed upon the TPI test but particularly upon a new specific test for syphilis – the fluorescent treponemal antibody absorbed (FTA-ABS) test.

The purpose of this report is to review advances in the diagnosis of syphilis and to emphasize that a *negative* blood test does *not* rule out syphilis. It has been known for many years that late syphilis commonly affects the eye and brain and may lead to blindness, paralysis, and insanity. However, with the advent of penicillin in 1943, and the widespread use of the conventional (reagin) blood tests for syphilis, it was thought by many that late manifestations of this disease no longer constituted a formidable problem. As a consequence little attention was paid to tertiary or late syphilis in medical education during the past two decades. It became common practice for many physicians to order a routine blood test and if this were negative, the possibility of syphilis as a cause for the patient's complaints was usually dismissed from further consideration. The fallacy of such reasoning, however, has been stressed by a cooperative study done by the University of Miami School of Medicine and the Venereal Disease Research Laboratory of the United States Public Health Service during the past three years. A new, more sensitive, and highly specific blood test for syphilis—the fluorescent treponemal antibody absorbed (FTA-ABS) test—has led to the discovery of over 200 cases of late syphilis in one hospital alone in the past two years.

In order to appreciate the importance of this finding, a few comments are necessary concerning the common types of blood tests for syphilis. Around 1941 Pangborn found that a chemical substance in beef heart would produce a typical reaction when exposed to the blood serum of a patient previously exposed to syphilis. The ingredient in beef heart was called "cardiolipin" and the substance in the patient's serum was termed "reagin". The cardiolipin antigen became widely employed thereafter and is used as the basis for all of the commonly employed routine blood tests for syphilis (the VDRL test, Kahn, Kline, Hinton, Mazzini, Eagle, Kolmer, and the like). These are therefore called the "reagin" tests. However, since such tests do not depend upon the specific organism that causes syphilis (Treponema pallidum) but upon beef heart, it was not surprising that certain patients showing positive reactions to the test were found indeed not to have had syphilis. These were called "biologic false positives" and other diseases (as the collagen vascular diseases, hepatitis, mononucleosis, and the like) were found to produce the falsely positive blood reagin test. However, the other side of the coin is statistically a much more common one, and is obviously more subtle and difficult to detect. That is—that many patients who have had totally untreated or inadequately treated late syphilis will show a negative (or normal) result to the conventional blood tests for syphilis! Thus, the term "seronegative syphilis" is used to connote this state. This problem has been further complicated by the widespread use of antibiotics in which patients have often received sufficient antibiotics for an upper respiratory infection, for example, to cause a weakly positive blood test to revert to negative, yet have not had an adequate treponemocidal course of therapy.

Two specific tests for treponema pallidum were utilized in this study: 1) the treponema pallidum immobilization (TPI) test, and 2) the FTA-ABS test. The latter is less expensive, appears to be at least as specific, and perhaps even more sensitive than the TPI test. In a study of over 1000 blood specimens drawn from patients seen on the Eye and Neurology services of Jackson Memorial Hospital in Miami, Florida during the past two years, over 200 cases have been found which meet the following criteria for seronegative syphilis:

(1) clinical signs of the disease, but with a negative blood reagin test
(2) a history of venereal infection, usually with inadequate treatment
(3) a reactive specific treponemal test (TPI or FTA-ABS). One can imagine the magnitude of this problem in the United States today if 200 cases have been uncovered in one metropolitan hospital.

Clinical signs indicating previous syphilitic infection have included: abnormal pupillary reactions to light, (light-near dissociation), optic atrophy, previous ocular inflammation, and certain characteristic findings on neurological examination. The presence of a greater pupillary contraction to light than to the near reflex has been associated with a reactive or positive FTA-ABS test in approximately 80% of the cases studied to date. About 60% of patients having traumatic or spontaneous dislocation of the lens in the eye as adults have shown reactive FTA-ABS tests to date. The spinal fluid has often been negative in patients with clinical signs of late seronegative ocular and neurosyphilis, and this is another important finding that merits further investigation.

It should be noted that laboratory studies of experimental ocular and neurosyphilis have been in progress in the rabbit and in two small species of monkeys during the past two years as well. These studies, although preliminary, have tended to corroborate the clinical findings described in man. Some animals inoculated with virulent treponema pallidum in both the eye and nervous system have remained clinically quite well during over 1½ year followup, and in some instances the animals have remained negative throughout this period of time to repeated blood reagin tests, yet both specific treponemal tests have become positive. The incidence of this phenomenon of seronegative active syphilis is now under active research. Further proof that such seronegative animals have been infected has been the successful recovery of treponema pallidum from them by transfer of blood or tissues to other, uninfected animals (usually rabbits).

Efforts are currently under way to have the FTA-ABS test performed at various State Health Departments, and thus this test should be available soon to the practitioner in this country. In the interim, the importance of a careful clinical examination of the eyes and nervous system cannot be overemphasized, for as has been known for some time, a careful history and physical examination are much more reliable tools in medical diagnosis than any laboratory tests. The FTA-ABS test holds great promise, however, for late syphilis affects not only the eye, but the brain, spinal cord, heart, and other organs and hence frequently presents with symptoms involving virtually every known medical specialty.

# OCULAR MOTILITY AND STRABISMUS

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There are six muscles in each orbit which insert upon the globe and move it. The twelve muscles for the two eyes are organized in a remarkable neuro-anatomical system which not only enables the individual eye to move right, left, up and down, but joins the two eyes together so that they make coordinated and equal movements in all directions. As a result of this yoking together, the two eyes are enabled to fixate an object of interest situated in the visual panorama and to follow that object of interest as it moves right or left, up or down. These parallel or conjugate movements are also referred to as versions. So long as the fixation and following reflexes in each eye are operative, enabling the sharpest point of visual acuity, the fovea, to be directed to the object of interest, the two eyes will simultaneously record the binocular visual image which will then be transmitted to the brain. In addition, should the object of interest approach or recede from the observer, the two eyes will make a disjunctive, nonconjugate or vergence movement, turning toward or away from each other in order to maintain sharp fixation upon it with both foveas.

For the proper and effortless functioning of this system of binocular fixation, there must be a certain anatomical substrate which must develop and function in a normal fashion. It requires in addition, a set of quasi-reflexes, sometimes called psycho-optical reflexes which through learning, usage and reward, enable the individual to obtain the benefit of a binocular image of the object of regard. The infant is born with the anatomical substrate but must develop coordination of the two eyes to achieve the necessary goal. At birth, this coordination is present in an imperfect form but within a matter of months it becomes firmly established in the pattern which will be utilized throughout life. If there is an anatomic or a physiologic impediment to coordinated activity of the two eyes, the desired goal of binocular single vision cannot be achieved. When the two eyes deviate from binocularity, the condition called strabismus is present. Strabismus may take many forms; in a common type, one or both eyes may turn in: This is called esotropia; one or both eyes may turn out: This is called exotropia; or there may be vertical or even cyclic deviations of the eyes. If the two eyes have developed normally and have been utilized in the normal fashion, the two retinas and their cortical projections in the brain become yoked together in a firm bond which enables one to gain a substantial goal, namely, binocular single vision. Binocular single vision differs from monocular vision in that it presents a fused right and left eyed view of the object of interest. This fused image has uniquely valuable properties. In consequence, the quality of stereopsis, or depth perception, becomes available to the individual, enabling him to make judgments of depth and relative distance with a degree of acuity lacking in one who must rely solely upon a monocular visual field. Stereopsis or depth perception, the so-called 3-D effect, is extremely valuable to the person who must compete in today's highly technological civilization. Our present knowledge of the nature of fusion is still highly fragmentary, although considerable research effort is directed at this problem.

What happens to vision when strabismus develops? The individual will see an object of interest in his visual field as doubled (diplopia). Such double vision is very disturbing both to the baby and to the adult. With the passage of time, through a curious process of selective inhibition of vision in one eye, called suppression, one of the images may be removed from consciousness. Suppression in childhood develops shortly after strabismus has occurred. The adult, however, with acquired strabismus, may never be able to get rid of the diplopic image. The image selected for suppression may proceed from an eye that has a higher refractive error or some impediment in its visual mechanism. If the two eyes are otherwise equivalent visually, dominance may govern the suppression of one eye. For a period of time suppression is facultative, that is, it exists only so long as both eyes are open. The deviating eye retains its normal visual acuity. If one eye is habitually deviated and the other eye utilized for fixation, the deviated eye whose vision is suppressed may undergo an alteration in the nature of that inhibition such that it becomes obligatory. When vision is tested in the deviating eye it will be found that the visual acuity which may have been perfectly normal prior to the onset of strabismus and for a short time thereafter, now has deteriorated and the degree of this deterioration may, in some instances, extend to the mere perception of light. The loss of visual acuity in the deviating eye in strabismus is referred to as suppression amblyopia. It is a curious phenomenon that if the good eye is kept covered and the deviating eye utilized for fixation, after a period of time the visual acuity will return to or achieve the normal level. This is the basis of the occlusion treatment of amblyopia. Until the past decade, it was felt that amblyopia which persisted beyond the age of six or seven could not be reversed so that it was critical to recognize the existence of strabismus and amblyopia in the child prior to that age. Occlusion therapy of the better eye, would result in improved visual acuity in most, if not all, such young children. With the work of Bangerter and Cüppers in Europe, the classic concepts and treatment of this condition were altered. They found that not only was there a decrease in visual acuity in amblyopia, but that the normal foveal fixation of the eye might also deviate to some eccentric point which anatomically and physiologically would be incapable of normal visual acuity. Such eccentric fixation is encountered in a very considerable percentage of amblyopia. It has long been known that a blind spot or scotoma in the visual field corresponding to the fovea and eccentric fixation area is characteristically present in amblyopia so that the loss of vision could be attributed both to the scotoma and to the eccentric fixation of such eyes. Pleoptic therapy, the term applied to a wide variety of retraining methods, was introduced by Bangerter and Cüppers and has had wide acceptance around the world. Unfortunately, pleoptic therapy does not work in all cases, and the percentage of good results varies greatly in different laboratories with different workers. A significant aspect of this therapy is that it is not limited by the age of the individual but even in adults an amblyopic eye may be restored to a better degree of visual acuity in many instances.

It is still better to prevent amblyopia before the age of six or seven than to have to rely upon pleoptic therapy at a later age. It is helpful to think of the visual acuity as a mountain of vision rising out of a sea of relative blindness. The peak of the mountain represents the normal acuity of approximately 20/20. With the onset of amblyopia the mountain sinks into the sea until all that is left is the surrounding area of acuity which is intrinsically poor. With therapy of amblyopia, the mountain rises out of the sea until it achieves its normal peak of 20/20.

The study of amblyopia has been approached on many psychophysical and electrophysiological lines. The EEG has been shown in some cases to be abnormal. Retinal and retinal-cortical factors have been implicated by various tests although the exact locus of the disturbance has not been clearly defined. The fact that amblyopia affects a high percentage of the people of the world constituting an important international cause of monocular blindness, makes it imperative that intensive studies be carried out against this form of blinding disorder.

In thinking about strabismus one is struck by the remarkable fact that with so many forces and factors required to coordinate the movements of the two eyes into a single functional unit, so many people have learned to accomplish it. It is clear that with a knowledge of the basic physiopathology of muscle and of brain control mechanisms, man ought to learn how to restore to normal binocularity significant numbers of those who have failed to achieve it. Although surgery in strabismus is often very effective in accomplishing a cosmetic cure, which is of course, extremely important to parents and child alike, a functional cure is far less frequently accomplished. The ophthalmologist today attempts to achieve not only a cosmetic but a functional cure of strabismus. With improved understanding of the basic mechanisms underlying ocular motility and binocularity, it is reasonable to expect that we shall some day achieve a far better therapy of crossed eyes. Medical measures may ultimately largely replace surgery in comitant strabismus. This has been amply demonstrated in accommodative strabismus where anti-cholinesterase drugs and glasses have proved extremely effective.

# AMBLYOPIA

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As science writers, you can be of real service in helping prevent the widespread and unnecessary impairment of vision that results from several related eye conditions grouped together as "amblyopia". There are now about 2 million Americans who have this kind of vision loss, and most of these cases could have been prevented.

The term "amblyopia" is derived from the Greek and means "weak" or "dull" vision. In ophthalmology this term is usually applied to conditions causing reduced vision in the absence of known eye disease, past or present.

There are two main types of amblyopia: one occurs when the retina is not sufficiently stimulated during infancy; the other results when the brain receives confused or unequal images from the retinas of the two eyes.

The first type, from insufficient light stimulation in the early years, is less common but still important. Like other organs, the eye must receive adequate stimulus and use in order to develop properly. (The human eye is seldom injured by excessive use, but it can be harmed by under-use.) For example: the presence of a cloudy or opaque lens from infantile cataract, or an opaque cornea from infection or hereditary causes, can shut off the necessary retinal light stimulation. If the condition is not corrected early enough, permanent impairment—and actual blindness—can result.

The more common forms of amblyopia, however, are the result not of understimulation but of unequal or confused images on the two retinas. Normal binocular vision takes place, of course, by the *fusion* (into a single image) of the two similar images of an object perceived by the two retinas. This fusion process takes place at the higher visual centers in the occipital area at the back of the brain. There are many ways this fusion process can be interfered with — all the way from too much alcohol to a blow on the head — but there are two main types of interference in the group of conditions called "amblyopia".

The first results from imbalance of the eye muscles, which causes strabismus — commonly called "squint" or "crossed eyes". Various types of muscle imbalance cause the affected eye to deviate from its normal positions—whether inward or outward, up or down. And when one eye is deviated, a given portion of the retina of that eye is seeing one thing while the same area of the other retina is seeing something else. Naturally, this disparity of images between the two retinas causes difficulty at the higher visual centers. To offset this problem, the brain apparently suppresses the image from the deviating eye. But this is an imperfect solution: if the condition is not corrected by the age of 3 or 4, this suppression can lead to changes in the visual system that result in permanent impairment of vision. In some "squinters" this inhibition ceases as soon as either eye is covered, and normal vision is present when the patient looks with one eye only. However, in others the inhibition persists, and visual acuity is found to be markedly reduced in the squinting eye when the fellow eye is covered.

In the other form of visual fusion problem in amblyopia, the difficulty is not (as in strabismus) the fact that a given location on the two retinas is perceiving a different image; the problem is that the two images, although of the same object, are of unequal size. This results when the refractive or focusing power of the two eyes is unequal. This can happen when the two corneas are of markedly different curvature, or if one eyeball is longer than the other, or if the lens is absent from one eye because of removal of a cataract.

Technically, this inequality in apparent size of an object as seen by the two eyes is called *anisometropia*, which is from the Greek and means simply "not having the same size, or measure". Again, the brain compensates by suppressing one of the images, and the resultant changes in the visual system can lead to permanent impairment.

Taking these three main forms of amblyopia together — understimulation, image confusion from the eye deviation of strabismus, and the unequal images of anisometropia—the incidence of amblyopia in the United States has been reported to range between one and two percent. (Both major forms of amblyopia, the strabismic and the anisometropic, occur with about equal frequency.) This means that nearly two million people in this country are affected by this form of visual loss.

The consequences of being amblyopic are manifold. Loss of binocularity usually occurs, i.e., the eyes will no longer work as a team, and most of the sensory advantages of being able to use both eyes together are lost. For instance, an amblyopic patient will rarely have depth perception, and this will exclude him from an increasing number of vocations in our technological age. While such a person may ordinarily adjust himself to this condition, the situation becomes more dramatic and serious if the good eye loses its function through disease or injury. In such instances, the amblyope cannot rely, like a normal person, on the second eye as a "visual spare tire" but becomes, for all practical purposes, blind. Thus, two million Americans can be considered potentially blind in such circumstances. And they may not even be aware of their condition; many persons with a squint, for example, may not know that vision in one of their eyes has been damaged as a result.

The reason that the problem of amblyopia has been selected for presentation to this audience is twofold. Recent clinical investigations have demonstrated that amblyopia, in contrast to other ocular diseases, is a condition that is almost completely preventable if it is discovered and treated early in life. In children up to the age of four years, amblyopia can be cured in almost every instance by proper therapy. In older children this becomes more difficult, and in adults largely impossible. Not enough can be done to alert the public — to educate nurses, teachers, and parents — and even to inform the non-ophthalmological part of the medical profession on this subject. Children with strabismic amblyopia must come to the attention of the ophthalmologist at an early age when they can still be treated effectively. The old erroneous notion that strabismus usually outgrows itself, or does not need to be corrected until school age, must be eliminated. Treatment for eye-muscle imbalance and thus for its consequence, the amblyopic eye, is possible in any child after the age of six months.

Anisometropic amblyopia is a much greater problem in prevention. Although strabismus may develop secondarily in these cases and such children may therefore be seen eventually by an ophthalmologist, many of these children appear to have completely normal eyes, and they are not diagnosed until their school entrance examination. To prevent this form of amblyopic damage, it would be ideal to be able to do a routine vision test in all children at the age of three years. Many diseases that formerly presented a great hazard to the health of our children are now controlled by effective and widespread prevention programs through early immunization. On the other hand, a complete examination of the eyes by a competent ophthalmologist, which could prevent permanent loss of visual function of one eye from amblyopia, is often not thought to be a necessary part of an effective preventive program during infancy and childhood.

The second reason for reporting to you on amblyopia is to stress some of the research possibilities in exploring its causes and mechanism. Until we have stamped out amblyopia by preventing it early in life, we are faced with the difficult problem of trying to treat it effectively in the older child and in the adult patient who has lost his one good eye. So far, all therapeutic methods have been rather disappointing to us as physicians. This may partly be due to the fact that the mechanism of amblyopia is still poorly understood. We have learned in recent years a great deal about its clinical manifestations, and we have come to the conclusion that reduction of visual acuity is only a small part of a syndrome that is characterized by manifold defects involving not only the sensory but also the motor part of the visual apparatus and the higher connections in the brain.

One reason that our knowledge of the mechanism of amblyopia, and its actual seat in the visual pathways, is so incomplete is perhaps the fact that previous investigative work has been limited to the study of this condition in human patients. Now, however, the newer techniques in neurophysiological research, such as single cell-unit recordings by means of microelectrodes in various parts of the visual system in animals, may begin to shed more light on this problem. Such work has recently been performed by Hubel and Wiesel at Harvard, who demonstrated for the first time that deprivation of normal visual stimulation in visually immature kittens can lead to actual cellular and functional changes in some parts of the brain. While the results of such basic work in lower animals cannot automatically be applied to the problem of amblyopia as it occurs in humans, the data published by these authors are nevertheless most exciting and point the way for future work in this direction.

At the Wilmer Institute, we are in the initial stage of a project that involves the study of the effects on the visual apparatus, in monkeys, of light and form deprivation and of strabismus artificially produced in the early days of life. We expect that the results of this and other projected research in primates will eventually provide us with better understanding of the mechanisms of vision loss from amblyopia, and we hope this will enable us in due time to improve our methods of treatment and prevention.

# APPLICATION OF GENETICS TO OPHTHALMIC RESEARCH

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The ophthalmologist has acknowledged that human genetics is not merely a study of remote human ocular peculiarities but rather that it opens an avenue of investigation into the exciting ferment of current medical problems. Genetics has been given an established position in modern biology. It has served to critically appraise, solve in part, and formulate both old and new concepts. Genetics today is of great theoretical interest and of great significance for human life, both in areas of accepted knowledge and where its application is still uncertain.

I am assuming that my audience has a working acquaintanceship with the basic tenets of genetics, but even so perhaps a few minutes may be well spent in review. Basically, genetics is a study of individual differences. Such variations are based on individualistic differences in the chromosomes of the cell nuclei and of their basic units—the genes. Actually all manifestations of life are influenced in varying degree and subtle interplay by these genes. By definition a gene is a unit of heredity, a highly complex problem molecule comprised largely of DNA. These genes are linearly localized on chromosomes and are capable of replication, assortment and independence. The chromosomes are present in all cells, are duplicate in number (human 23 pairs) except in the mature sex cells. The laws of transmission by which genes are transferred from generation to generation are simple and valid. The laws of transmission of genes are somewhat independent of the effect of the genes since the latter are manifold, complex, and rely on intimate interplay between the gene-enzyme and environment. In human genetics we study the differences as well as similarities due to genes and chromosomes but we must also take into consideration these environmental influences which have modifying influence on all final products. *No one gene acts alone*—in fact its end product is the result or combination of effects of the entire gene milieu modified by a myriad of environmental factors. To study and analyze these variations such disciplines as biochemistry, cytology, teratology, serology, immunology, and physiology are utilized by the geneticist. Genetics thus serves as the liaison catalyst in the intimate and utilitarian marriage between the practicing physician and the research laboratory.

Since our time is limited today we shall take up approximately six phases of genetic research and its application in ophthalmology.

## I. Epidemiology

Epidemiological studies (the science of

epidemics or the treating of disease) have revealed that certain hereditary diseases may be found in a specific population, or isolated, and reflect thereby the consequence of an interaction of the genetic forces of *mutation* and *selection.*

A cerebrophospholipoidosis, Tay-Sachs disease, or amaurotic infantile idiocy, presents clinically diagnostic features among which is an ophthalmoscopically observed "cherry red spot" in the macular area of the eye. Careful pooling of family data has revealed that Tay-Sachs occurs more frequently among Ashkenazic Jews than among other populations. It has been proven that these people have a heightened incidence of this mutant gene in their population. Aronson et al (1962) performed laboratory tests which disclosed a deficiency of the enzyme fuctose-1-phosphate-aldolase in the blood of a parent of afflicted children, thus constituting a test by which carriers of the gene could be detected. This is a subject which we shall discuss later. Subsequent study indicated carrier rates of 20/1000 for the Ashkenazic Jews and 3/1000 for other Jewish populations. Such an elevated gene frequency in a specific population may be explained by entertaining two possibilities: (1) A high mutation rate in this specific isolate—but this is unlikely since it would necessitate a mutation rate of nearly 50 times the highest known human mutation rate for any disease or for that matter of laboratory animal disease. (2) Genetic drift may occur in small populations, perhaps merely by chance, because of a concentration of carriers for this recessive gene. Such chance concentration may develop as a consequence of *genetic drifts.* Such gene frequencies may be interpreted in two opposite lights: (1) It may be assumed that the gene is selectively neutral, thus the result of simple mixture of ancestral groups which in turn must be presumed to have been genetically identical; how, in the absence of differences in fitness, the original groups can differ in the gene frequency is not clear, unless by drifts. (2) On the other hand, one may assume that certain characters in the population may have strong selective significance and the genes responsible for these to have strong selective forces. It is difficult to see how the heterozygote state of this gene may have had strong and favorable selective value to preservation of the individual. In the lack of exact knowledge the high evidence of Tay-Sachs disease in this isolate will have to be accepted on the basis of chance and on original small population, thus genetic drift.

### II. Cytogenetic Studies

Cytogenic studies have disclosed an association of ocular disease and specific chromosome aberration. Chromosomes during meiosis and/or mitosis may fail to separate—nondisjunction, or suffer loss of a portion—deletion, or duplications of chromosome regions (translocation), and/or reunion in a new way—inversions. Such changes always influence alteration in the quantity of the duomosomal material which results in new phenotypes—mutation. Chromosomes are visible as discrete nuclear bodies during cell division. Recent advances in cytology—tissue and cell culture, improved treatment of dividing cells with colchicine (squash technique) whereby chromosomes in the metaphase state of cell division can be stained and identified, particularly on the basis of their relative size and centromeric position which permit grouping into seven series. Those groups have arbitrarily classified into groups A through G. Such pairing of chromosomes and the resultant composite is called an *idiogram.*

Careful study of those idiograms has revealed aberration of structure, number, form and composition of the chromosomes. Among the disturbances in the number of chromosomes is the autosomal defect known as Down's syndrome, or mongolism. Early in this century, an ophthalmologist, Dr. Peter J. Waardenburg postulated that this disorder was the consequence of a chromosome aberration. Subsequent study has supported his hypothesis. Mongolism is a form of mental retardation in which many ocular signs may be present in association with a vast number of systemic alterations, to wit: epicanthus, strabismus, dacryocystitis, mesodermal iris (Bruchfield's spots) structural changes, and typical cataracts. Chromosome studies in sporadic cases of mongolism—generalized retardation of development — usually exhibit 47 chromosomes, the extra chromosome in idiograms being presumed to be number 21 (Group G). Some authorities identify number 21 because of the presence of a satellite—knob of chromosome—on one end. It is assumed that the mother produced ova containing either 23 or 24 chromosomes, the result of meiotic nondisjunction. Another form of mongolism exists—the translocation form. In this variety the chromosome count is 46, but the karyotype is abnormal in that an extra chromosome in Group C and deficiency of one in Group D exists. Further study reveals that chromosome 21 is attached to 15 and the latter product looks like a chromosome of Group C—reciprocal translocation.

Other autosomal chromosomal trisomies are known and exhibit ocular manifestations—trisomy D and trisomy E. Translocation forms of these trisomies are known also. It is interesting to note that an unusually high incidence of chromosomal aberration occurs in the fetal remnants of abortions.

### III. Mutation

The fact that mutation may produce a structural modification in a protein was discovered in studies on the disease known as sickle-cell anemia. This disease exhibits a recessive mode of inheritance of a chronic severe hemolytic anemia. The disease may effect retinal vascular alterations and retinal and vitreous hemorrhages. Pauling and his co-workers (1949) found that hemoglobin in the erythrocytes in sickle-cell anemia patients was not normal. In the presence of lowered oxygen the molecules of this abnormal hemoglobin aggregate into rigid structure, giving the cell a bizarre sickle-like shape. It was hypothesized that this reaction was related to an altered surface electrical charge on the molecule and furthermore assumed that the mobility of such a hemoglobin would be altered in an electric field. Electrophoretic studies eventually disclosed that the iso-electric point of normal hemoglobin was 6.87 and that of sickle-cell hemoglobin was 7.09. These same workers further assumed that the altered hemoglobin was due to an allelic (gene) change in a single gene; in fact, a change in a cellular protein molecule. Further research uncovered the fact that the fault did not lie in the heme groups but rather in the globin and that only one glutamic acid residue is replaced by a valine residue. This minute difference results in sickle-cell anemia. Subsequent studies have uncovered numerous molecular mutations—many having ocular manifestations—for example, sickle-cell and C disease and sickle-cell and D disease. It is to be emphasized that mutation thus can be the consequence of a minute subtle change in protein structure.

### IV. One Gene—One Enzyme

"Genes act by regulating chemical events." After intensive study of the eye pigments of the fruit fly—Drosophilia, Beadle and later Tatum, chose a fungus Neurosposa by which to investigate genetic enzymatic defects. This fungus was most aptly chosen since it had simple nutritional requirements which made for efficient study of its amino acid and vitamin metabolism. By inducing mutations in this organism and by growing it on media supplemented with a variety of vitamins and amino acids, or without supplements, it was possible for these investigators to detect deficient strains which had lost the ability to synthesize one or more of the substances in the media. A series of systematized experiments disclosed whether the nutritional deficiencies were the result of mutations and/or of single gene mutations. These investigations eventually substantiated the concept that genes have primary functions in addition to self replication—namely, to direct specific enzyme activities, thus the one gene - one enzyme theory. In essence the synthesis of a compound thus becomes the result of successive enzymatically catalyzed steps leading to the end product.

Even prior to Beadle and Tatum's work Sir Archibald E. Garrod became interested in a group of human congenital metabolic diseases. In fact he eventually coined the term "inborn error of metabolism" for this group of disorders. In his study of Alkaptonuria—a disease caused by the inability of an individual to split the ring of homogentisic acid as do normal individuals—he found that this mobility was due to an absence of the enzyme which normally catalyzes this action. Garrod recognized that failure to metabolize an intermediate compound, when its normal pathway was blocked by a gene-enzyme defect, accounted for the accumulation and excretion of homogentisic acid. Today we recognize the ocular manifestations of a myriad of such inborn errors of metabolism and the ophthalmologist is in an extremely favorable position to be of diagnostic and prognostic help to the medical as well as laboratory professions. Homocystinuria, a recently discovered error of metabolism, was found in this country by an alert ophthalmologist who detected the association of dislocated lenses with mental retardation, adermatosis, amino-aciduria, and so forth.

### V. Genetic Carrier States

Genetic studies of families in which hereditary diseases exist require the most meticulous clinical and laboratory investigation since in many affected individuals the changes may be only extremely mild or subtle expressions of the gene effect. Therefore the development of techniques for the detection of genetic carriers of hereditary disease is both theoretically significant and practically important. A "carrier state", for our purposes, may be defined as arising under the following genetic situations. (1) An autosomal gene produces a severe disease in homozygotes but has mild effects in heterozygotes. Examples to be illustrated include: *a.* Ehler-Danlos syndrome; *b.* albinism; *c.* xeroderma pigmentosa; *d.* phakomatoses; *e.* Marfan's syndrome, and *f.* galactosemia. (2) A sex-linked (x-chromosome) gene produces a severe pathological effect in males but has minor subclinical effects in heterozygous women. These include: *a.* choroideremia; *b.* sex-linked albinism; *c.* chorioretinal atrophy; *d.* keratosis follicularis spinulosa ophiasis; *e.* external ophthalmoplegia, and *f.* congenital ectodermal dysplasia. (3) An autosomal gene produces symptoms in some heterozygotes but has some minor nonpathological manifestations in other heterozygotes. Under the last may be included carrier states recognized in individuals of different sex or earlier age than those who show disease symptoms. These include the following: *a.* diabetes; *b.* gout; *c.* hypercholesterolemia; *d.* Fuchs' epithelial-endothelial dystrophy, and *e.* primary glaucoma.

### VI. Therapeutics

As previously intimated, biochemical investigation of metabolic disease has contributed to an understanding of genetics and in turn the application of the latter has led to better understanding of metabolic processes. This is true especially of protein metabolism studies, which led to the theory of one gene-one enzyme, one enzyme-one protein, and more recently one enzyme-one polypeptide. Despite our inability, at least to date, to induce enzyme formation in such enzyme deficient individuals, circumventing procedures can aid in controlling the availability of potentially harmful substitutes, thus improving the prospect of eventual helpful therapeusis.

It is necessary, of course, to emphasize that the treatment of hereditary disease, as mentioned above, can be instigated by the following procedures: (1) Surgery for: *a.* keratoconus; *b.* corneal scarring; *c.* strabismus; *d.* glaucoma; *e.* cataract, and *f.* eyelid defects (colobomata and ptosis). (2) Medical correction for: *a.* galactosemia; *b.* phenylketonuria, and *c.* questionably homocystinuria. (3) Theoretically we may change a protein. Possibilities include supplying a missing protein or modifying a defective one. In my own work to date I have not been successful in stimulating melanin pigment formation in albinos. The future holds great promise, however, that synthesis of a missing or altered enzyme can be supplied by activating a regulator gene, or even altering a structural one. As early as five years ago we could not have dreamed of such a prospect. Definitive therapeusis actually may not be too far in the future.

# THE ROLE OF EYE MUSCLE IMBALANCES IN READING PROBLEMS

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Reading difficulties and the so-called problem reader are a matter of increasing concern to educators. It is estimated that 20-30% of school children have subnormal reading ability.

The purpose of this paper is to call your attention to one segment of the group of these children. This specific segment has eye muscle imbalances considered to be causative of their difficulty. Surgical treatment resulted in elimination of the imbalances and in turn gave invariable improvement in reading performance. Many of these children had had various methods of preceding treatment, all unsuccessful.

A child may have a reading problem from a wide variety of causes. A classification of dyslexia (impairment of the ability to read) based on causes results in three general groupings:

### Group I.

Difficulty due to subnormal intelligence. The problem here is simple incapacity to learn and is not a reading problem as such.

### Group II.

Difficulty in a child with normal or above normal intelligence secondary to a demonstrable cause. These causes include: 1) emotional factors, pre-school or school; 2) physical factors (visual, auditory, glandular, slow maturation, gross brain damage); 3) educational factors.

This group is referred to as having secondary reading retardation, or a corrective reading problem. It constitutes approximately 80-90% of retarded readers. The prognosis for successful therapy in this group is good when the specific cause is found and remedied. The series we studied is in this group.

**Group III.**

Difficulty in a child with normal or above normal intelligence when no demonstrable cause can be found. This group makes up the remaining 10-20%, and is referred to as having specific dyslexia, congenital word-blindness, strephosymbolia or a remedial reading problem. Many of these children have evidence of subclinical brain damage as shown by abnormal electroencephalograms. They often show delayed handedness, mirror writing, poor spatial orientation (visual-perception dysfunction), emotional instability, clumsy physical coordination. Hypoxia or anoxia (deficient oxygen) is considered by many to be the probable cause or at least a factor. An hereditary factor exists in some instances. The role of crossed or mixed dominance as a causative factor is highly controversial but the majority of studies done indicate it is not causative. The prognosis for successful treatment in this group is poor. The sex incidence shows a ratio of at least two males to every female.

It is important to realize that many children cannot be precisely categorized, and that multiple factors can and often do exist. The commonest finding in both groups is a psychological and emotional element of some form or other and of varying intensity. Most of these children have a sense of inferiority by virtue of their difficulties having brought criticism at both home and school. This in turn creates further emotional difficulty and a vicious circle is set up. The most important overall needs in the therapy of any of these children are motivation, patience, constant encouragement, early treatment, and the elimination of any demonstrable factor if possible.

As stated, our interest and work lie with a sub-group of Group II; namely, children of normal or above normal intelligence having the demonstrable defect of an eye muscle imbalance. This imbalance need not be large; in fact, many of them are quantitatively very small. Why such defects act in this way only in some children is not known. The most important and characteristic feature we found in our study was that the eye muscle imbalances were controlled at least part-time. We feel *it is the work required by the individual to control this defect that leads to inefficient reading mechanics.* Children with uncontrolled muscle imbalances do not have reading difficulties—they function as one-eyed individuals, putting out no work to attain or effect binocular vision and thus having no problem.

We have a series of 40 patients treated surgically and followed from one to three years. There was invariably immediate or early improvement in measured reading performance, subjective reading comfort, scholastic improvement, or emotional betterment. Most of these children had had periods ranging from a few months to over five years of various forms of training and exercising, without aid. Some had been labeled as mentally retarded. Many had failed one or more years of school. The majority (83%) of our series had a combination of horizontal and vertical components, and most of them (66%) were exophoric (outward turn tendency). One child had a vertical imbalance alone. This distribution does not parallel the general incidence of muscle imbalances; the occurrence of exophoria in children in our group is abnormally high.

This concept of surgery for children with reading problems associated with small muscle imbalances has been largely disregarded by most ophthalmologists, probably due to either fear of surgical overcorrection, or to the belief that if the imbalance is small and at least partially controlled it cannot be causative, or to failure to find small imbalances on routine examination.

It MUST be remembered that eye muscle surgery is NOT being recommended for all children with reading problems, nor as a cure-all for every type of defect; but it IS advised when a muscle imbalance, no matter how small, can be elicited and when no other factor exists. It is our opinion based on our case records that exercises, so-called exercises, and reading training are ineffective in this group. While this form of reading problem constitutes a relatively small percentage (estimated at 10-15%) of the total number of children with reading difficulty, it is a group that can be cured or at least significantly aided.

A closing word on reading difficulties in general is that there is great confusion today in the therapy of this problem. Educators, psychologists, and medical personnel are each involved but there is little coordination of either research or approaches to therapy. From both research and clinical standpoints, there is great need for a coordinated effort by these three groups to meet this problem more effectively. This would best be effected by the establishment of widespread centers to encompass diagnosis, therapy, and research. Teams should be composed of educators, psychologists, reading teachers, orthoptists, general medical doctors, and various medical specialists. These centers can best be established in conjunction with existent medical centers. This would promote efficient and thorough care. This approach would be expensive, but it would more efficiently handle a problem that currently is being haphazardly approached on a rather disorganized basis, with educator, psychologist, and doctor each going his own way. In view of the current philosophy and practice of government grants both for research and patient care, and in view of the enormity of the problem and its long range effect on the educational level of our public, the potential results could well justify the cost. It is not unreasonable to consider and even request the institution of such a program, isolated or incorporated in some current facility.

# CORNEAL DISEASES
# INCLUDING THE USE OF PLASTIC CORNEAS

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The importance of the cornea to the visual process is obvious since it is the first surface of the eye presented to the incoming light ray. Consequently a disturbance in this area automatically interferes with vision no matter how good the rest of the eye may be. The cornea can be affected by a disease process in the same manner as all other tissues of the body. These include congenital abnormalities, injuries, infectious disease, degenerations or dystrophies, and cancer.

In most instances little can be done about congenital deformities of the cornea. Usually they are accompanied by other deformities so that even if the cornea were clear it is not likely that the individual would have much useful vision. In an occasional instance there may be some place for corneal transplantation. Control of this particular problem lies more in the realm of genetics, control of conception, and prevention of prenatal disease in the mother.

Injuries of the cornea we will have with us as long as we have war, high speed transportation, heavy machinery, and human carelessness.

Infectious diseases which used to account for a high percentage of corneal ulcers, opacities and perforations with ultimate loss of the eye, have been remarkably reduced in quantity since the advent of antibiotics. In general, bacterial infections play a relatively minor role in present day corneal disease, most, in the absence of neglect, being readily controlled by available agents. There remain, however, virus and fungal diseases, none of which can be readily controlled by the current medications.

Like virus disease, fungal infections of the cornea have been increasing rapidly in the past few years probably associated with the expanded use of antibiotics and steroids. Since medications available for use in this condition are far from satisfactory, fungus keratitis remains one of our major problems.

Degenerations of the senile type and dystrophies, which are ordinarily loosely defined as a defect of nutrition to an area, are usually localized and not associated with any inflammatory or known disease. They are completely resistant to prevention.

There remains then the problem of corneal transplantation both as a means of controlling active infection and as a method of repairing a scarred cornea which has been the scene of a bacterial, viral or fungal infection.

Contrary to the great problems associated with the grafting of tissues elsewhere in the body, homo-grafting of corneal tissue has been a clinically successful procedure for over 60 years. Clear, functioning transplants are a common occurrence, the percentage of success varying with the state of the host tissue into which the graft is implanted. Current thinking suggests that the cornea occupies an immunologically privileged position in the body in that it has no direct connection with blood vessels and consequently has, under normal conditions, little contact with cells of the lymphocytic series. It is the general feeling that grafted corneas persist in the host as a true chimera, the cells of the donor living and maintaining their identity while occupying space in the new host. This is of course a most unusual biological phenomenon which is ordinarily attributed to the unique anatomical and physiological position of the cornea.

Although corneal transplantation is ordinarily a successful procedure, there remains a rather large number of patients with corneal disease in whom keratoplasty does not result in useful vision for reasons not clearly understood. Such grafts either become opaque, heavily vascularized, or both. It is to help these otherwise hopelessly blind individuals that, in recent years, there has been a resurgence of interest in artificial corneas.

The idea is by no means new. There are references in the literature suggesting that artificial corneas were proposed in the late eighteenth century. Over a hundred years ago a glass plate was successfully retained in a rabbit cornea for three years. Similar reports appeared thereafter with increasing frequency. Most or all of these implants ultimately were extruded, the almost universal fate of exteriorized prosthetic devices elsewhere in the body. With the development of acrylic and silicone compounds, which have proved to be relatively inert, the past ten to fifteen years has witnessed independent developments in various parts of the globe. Recent contributors to the field have been the Barraquers, Stone, Strampelli and Cardona.

Although the sizes, shapes and composition of corneal prostheses are almost unlimited, they in general fall into three major types:

1) *Intralamellar* implants are inserted between the layers of the cornea and are not exposed to the exterior or interior of the eye at any point. These have been used largely to change the refractive error of the cornea or to alter fluid exchange between the anterior chamber and the cornea in certain conditions which are characterized by edema. In general, success has not been outstanding for either condition. It may be, however, that synthesis of new materials with different capacities for passing electrolytes and fluid may alter this picture.

2) In the *partial penetrating* keratoprosthesis, the central supporting flange of the prosthesis is inserted intralamellarly as in the previous case with the exception that a perforation is made into the anterior chamber posteriorly through which an optical cylinder extends. Such a device may be used when the anterior cornea is clear but the posterior cornea heavily scarred. Alternatively, a lamellar keratoplasty can be performed combined with the insertion of such an implant. The practical problem here is that in such situations the overlying graft ordinarily becomes opaque.

3) *Penetrating* keratoprosthesis is usually preferred, its general principles being the same but the modifications innumerable. In essence, the device is composed

of a central cylinder ground with optical surfaces to project an image upon the retina. This cylinder extends throughout the full depth of the cornea and is in contact with the tear film anteriorly and the aqueous of the anterior chamber posteriorly. The cylinder is supported by various appendages which may be in the form of a ring, a plate, or bar attached to the cylinder. These projections have the dual purpose of supporting the implant and making a water tight seal around the cylinder.

For the cylinder, materials used have been glass, methylmethacrylate or silicone. The supporting part of the device has been made of silver, gold, platinum, glass, methylmethacrylate, silicone, bone, tooth, toenail, nylon, dacron and doubtless numerous other materials. Almost universally such operating is now done using the operating microscope. The development of suitable operating microscopes is a field in itself, all those currently on the market being somewhat crude and awkward to handle. Several of the major optical and instrument companies are working intensively in this area and it is to be expected that in the near future a much more effective instrument will be available. With the development of such observing systems there has been a concurrent development of finer instrumentation permitting more delicate work.

The major complications associated with artificial corneas at the present time are as follows:

1) Extrusion of the implant is by far the most common and serious problem. Exteriorized keratoprostheses behave differently from those elsewhere in the body. They have been retained in animals for four to five years and equally long in human beings. This indicates that under proper circumstances it is possible to retain artificial corneas in the human eye for at least five years and presumably indefinitely. But we are not yet certain what constitutes proper circumstances.

On the other hand, in our series of 115 eyes about 20% of the implants have been extruded over a varying period of time. Such extrusion ordinarily takes the form of very slow dissolution of tissue adjacent to the cylinder of the implant. Since it is our feeling that this may be closely related to the local nutrition of the cornea and with the passage of fluids from the posterior cornea anteriorly, we are currently working with multiple materials hoping to find one which will permit such fluid transfer and still be an effective support.

2) The second most common complication is overgrowth of tissue either behind the posterior extension of the implant or over its anterior extension. It is for this reason that we have discarded flush surface prostheses both anteriorly and posteriorly and like to have a slightly raised surface so that epithelial cells with underlying fibroblasts do not cover the implant. This complication is ordinarily rectified by removing the implant and inserting one with slightly longer projections.

3) Infection is a most uncommon complication but as in any other surgical procedure is an ever present hazard.

Work with artificial corneas has now progressed to the point where animal work has relatively little use except in the preliminary trial of new materials. The animal eye is quite different from the human eye and what may work in the animal eye may not necessarily work in the human eye. And the opposite is also true. Therefore, further progress now requires human trial. In the present state of our knowledge we are employing the implant only in eyes that are otherwise hopelessly lost, eyes that have had multiple transplants and have failed, and those in which we know from previous experience that corneal transplantation is doomed to failure. In some of these individuals we have been able to give reading vision, as well as distance vision in the order of 20/25 for periods up to about four years. We feel that this is sufficient to justify further trial. We do not feel that the operation is justified in someone who has one normal eye or in one in whom chance of successful corneal transplantation is good.

It might be appropriate at this point to say a few words about keratomileusis. This ingenious technique devised by Jose Barraquer of Bogota, Colombia involves basically a lamellar transplantation. The donor cornea is first removed and frozen solid. This frozen cornea is then placed upon a lathe and an optical surface ground on it to correct the patient's calculated refractive error. The donor material is then thawed and sutured into place in the patient's prepared cornea. Corrections up to about +8 diopters of hyperopia and −20 diopters of myopia are possible by this technique. Its clinical application seems somewhat distant at the present time since relatively small degrees of ametropia can now be fairly easily corrected with ordinary spectacles or with contact lenses.

# SYSTEMIC DISEASES

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Ophthalmology—the branch of medical science that encompasses all knowledge concerning the eye, the visual system and disorders affecting these sensory structures—is closely related to the entire field of medicine because the eye and vision are affected by systemic diseases of virtually all types. There are, for example, ocular manifestations of generalized developmental disorders, endocrine and metabolic diseases, infections, neoplasms, degenerations and injuries. The ocular signs and symptoms associated with these systemic disorders provide a broad area of "partnership" and common interest between ophthalmology and the whole of medical science. Certainly, knowledge of these ocular manifestations often aids diagnosis and serves as a guide to the effectiveness of treatment of systemic disease, while an understanding of the underlying disorder offers insight into the etiology and pathogenesis of the ocular abnormality.

A major portion of vision impairment in the United States is related to the effects of systemic disease on the eye and related structures. For example, rubella (German measles) in pregnant women is a common cause of impaired vision in newborn infants, acute leukemia may lead to loss of vision in affected children,[1,2] diabetes mellitus is probably the most common cause of blindness in the United States and the ravages of occlusive vascular disease are responsible for significant vision decrease in elderly adults.[3] Extensive studies of these and other systemic diseases are in progress. Recently, however, a severe epidemic of rubella focused attention on this disorder and led to significant advances in knowledge. As a result, current concepts of this disease merit specific consideration.

The occurrence of severe congenital anomalies in newborn infants whose mothers had suffered attacks of rubella (German measles) in pregnancy was first observed by an Australian ophthalmologist, Dr. Norman M. Gregg, in 1941. Numerous observations since that time confirmed the association between maternal rubella and developmental anomalies in the offspring and prompted intensive study of this relationship during the extensive rubella epidemic that occurred throughout the United States during the first six months of 1964. The full extent of the epidemic is not known but, at 14 institutions participating in a collaborative study, a total of 6,161 pregnant women were studied during this period. Of these, 2,383 were known to be exposed to rubella, 121 developed frank clinical rubella and others undoubtedly had subclinical infection.[4]

The offspring of women who contracted rubella during pregnancy often developed infection with the virus. The rubella virus could frequently be isolated from the fetus (the developing organism) when therapeutic abortion was performed.[5,6] Furthermore, the virus often persisted as a chronic rubella infection which was present when infants were born at or shortly before full term. Recognized for the first time during this recent epidemic, the chronic form of rubella infection in the newborn was associated with a low birth weight, an enlarged liver and spleen, thrombocytopenia and bleeding tendencies.[4,7] Significantly a number of these infected newborn infants were still shedding the virus at the time of birth and during the first year of life. Thus, they acted as a source of contagion and rubella occurred in personnel exposed to these infants in the newborn nursery and pediatric wards.[6,8]

In addition to this persistent infection with the virus, a number of developmental anomalies were noted in infants whose mothers had developed rubella during pregnancy—particularly during the first trimester (the first 3 months) of pregnancy. Included in these were severe disturbances of the cardiovascular system (e.g., patent ductus anteriosus), defects in hearing, mental retardation and ocular abnormalities. Of particular importance to the ophthalmologist, the latter consisted of cataracts (opaque lenses of the eye), microphthalmos (an abnormally small size of the eye), defective development of the iris, and glaucoma (an abnormal elevation of pressure within the eye). A characteristic pigmentary abnormality of the retina, nystagmus (rhythmic movements of the eyes) and markedly decreased vision were other features of the "rubella syndrome."[9]

Developmental cataracts, occurring as a consequence of maternal rubella, have been noted in greater number since the rubella epidemic in 1964.[10] These may be unilateral (affect one eye only) but are usually bilateral (affect both eyes). These cataracts may involve the nucleus (central part) of the lens or produce opacities throughout all parts of the lens and, significantly, they may be stationary or progressive after birth. Frequently, these cataracts necessitate ocular surgery.

At UCLA, during the course of surgery on patients with "rubella cataracts," specimens of aqueous humor (fluid in the eye) are collected to determine the presence or absence of rubella virus within the eye. Cataracts are then removed with an aspiration procedure[11] that is modified to increase the safety of the operation. This modification employs a fine gauge needle which is passed through the cornea (the transparent portion of the outer layer of the eye) into the anterior chamber (the fluid filled space between the cornea and the lens). Fluid passing through this needle maintains the shape and form of the eye throughout the operation and assists with the removal of the cataract. A needle shaped knife then cuts the capsule (the outer layer) of the lens and the opaque lens material is aspirated or sucked from the eye through a second needle. At a later stage, it may be necessary to cut the remnants of the lens and its capsule to provide a clear optical pathway. The procedure, performed with the aid of an operating microscope, is carried out in an analogous fashion.

Even with these surgical methods, the prognosis for vision in infants with cataracts and other ocular defects associated with the "rubella syndrome" is guarded. In fact, congenital cataracts of all types were the leading cause of blindness in a group of children recently studied in California.[12]

With awareness of the incidence and

severity of the adverse effects of rubella infection during pregnancy, it is not surprising that gamma globulin would be given to pregnant women exposed to the disease. In the collaborative study, gamma globulin was given as prophylaxis to 149 women exposed to rubella during the first trimester of pregnancy.[4] The combined clinical and laboratory data from this series have not been published. However, in at least one woman who was exposed briefly to rubella during the critical first trimester of pregnancy, an injection of 20 cc. of gamma globulin on the day of the brief exposure did not prevent the maternal rash or the infection of the fetus.[5] Furthermore, experimental rubella infections in nonpregnant people have demonstrated that gamma globulin has little or no protective effect against infection and may in fact be detrimental in that it may mask the clinical manifestations and obscure the diagnosis while not preventing the virus infection.

It is evident that much more work needs to be done on the epidemiology of rubella, the prevention of infection during pregnancy and the treatment of the virus infection and developmental anomalies that occur in the affected infants.

## Summary

Ophthalmology is closely related to the entire field of medical science because the eye and the visual system are affected by generalized or systemic diseases of all types. In fact, a major portion of vision impairment and blindness in the United States is related to the effects of systemic disease on the eye and related structures. For example, conditions such as rubella (German measles) in pregnant women, acute leukemia in children, diabetes mellitus in adults and occlusive vascular disease in elderly people are important causes of vision loss. A recent epidemic of rubella has focused attention on this disorder and led to significant advances in knowledge. As a result, current concepts of this disease merit consideration.

The occurrence of severe congenital anomalies in newborn infants whose mothers had suffered attacks of rubella in pregnancy was first observed by an ophthalmologist in 1941. Prompted by this and other observations, pregnant women were studied during the United States rubella epidemic in 1964. The offspring of women who contracted rubella in pregnancy often became infected so that virus could be isolated from the fetus when therapeutic abortion was performed and was frequently shed for many months by infants born at full term. In addition to this persistent infection, a number of severe developmental defects were observed in the affected infants. These developmental defects are noted, the treatment of rubella cataracts is described and the prevention of maternal infection is reviewed.

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# VISION FROM SPACE

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Before discussing vision, we must be certain that we are on common grounds in terminology. When I speak of "seeing", I am talking about a complex process which involves intellect and experience as well as optics. We can recognize close friends at greater distances than casual acquaintances. We make this recognition on the basis of imaged clues with which we have become familiar at closer range. It is difficult to analyze all the clues available, but they include size, shape, color and motion, all in a particular combination with which our experience and intellect can tell us that we are "seeing" that friend.

Major Cooper "saw" things from orbit in this same way. He utilized available clues on his retinae, added intellect and experience and thus "saw" a railroad train, a vehicle on a dusty road, and other fascinating details. This should have been a shock to no one, but is was to many. Too few of us realize that even on earth we do not have to see rails, wheels, springs, couplers, and cowcatchers in order to recognize a train unless we have never before seen one and have to recognize it on the basis of a verbal description. All we really need is a long, solid dark line moving along another longer line. A steam locomotive adds another clue, the smoke appearing as a line diverging from one end of the moving dark line.

### Visual Capabilities in the Laboratory

Some of the retinal capabilities available to a man in space have been thoroughly investigated in the laboratory from a threshold standpoint, including light, contrast, minimum visible lines, minimum separable lights or lines and breaks in lines.

Some of these capabilities are truly amazing and some appear to be optically and physiologically "impossible". A few examples of laboratory-demonstrated capabilities follow:

1. The sensation of light can be evoked by a *single quantum* falling upon each of 5 retinal rod cells.
2. A difference in the intensity of light falling upon two rows of retinal cones can be perceived even if it is less than 0.9 per cent.
3. A single line can be perceived as such when its geometric image on the retina is only 1/30th of the diameter of a single retinal cone.
4. A break in the continuity of a line can be seen when it subtends an angle as little as two seconds.
5. Fifteen seconds of arc separation of two points can be discriminated.

### Physiologic Basis for Perception of Details

From what we know about the optics of the human eye, we know with certainty that resolution at the retina is not good enough to explain these human capabilities. Likewise, we know that the size of the retinal cone cell mosaic is a bit too coarse to explain the perceivable detail, even if the optics were perfect.

There are, however, some explanations for these amazing capabilities: some are physiological facts, others are theoretical. The "Stiles-Crawford effect" acts to augment contrast in the retina by minimizing the physiologic effectiveness of rays of light which are not normal to the retinal surface. This effect is due to "fiber optics" properties of the long thin cone cells found in the fovea and serves effectively to refine the blur at the level of the receptor cell.

Theory gives us other needed explanations. It is probable that there is a conditioning of the output of retinal cones so that nerve fibers representing adjacent cones actually carry slightly exaggerated messages of differences in the intensity of stimuli reaching each of these cones.

In addition to the problem of imperfect optics, physiologists have been faced with the difficulty of explanation of sharp vision in spite of fine rapid movements of the eyes. These movements are constantly present and therefore make it impossible to explain the visual act in the simple terms of a camera-film eyeball-retina analogy. As early as 1923 theorists began to view these movements as an aid to perception rather than a hindrance. It appears to me that further understanding will be gained as physiologists begin to get more insight into computer theory. The retina and the brain probably work to some extent like a "computer of average transients." They average the stimuli and reject the "noise" allowing perception of stimulus differences of a very low order. As with the computer, the more samples presented, the greater is the ability to clarify the significant signal. Thus, the fine eye movements allow large numbers of "samples" to be taken and give our computer mechanism more data with which to arrive at a refined perception in a brief time span.

### Basis for Misapprehension

For several decades we have had laboratory confirmation of capabilities such as were demonstrated by Astronaut Cooper and the Gemini Astronauts. Calculations show the following perceptions to be theoretically possible from an altitude of 100 miles (if we neglect the atmosphere and the spacecraft window):

1. A bright glint of light no matter how small the source or reflecting surface.
2. A sharply contrasting line as narrow as 1¼ feet (0.5 second or arc subtense minimum discriminable).
3. A break in a line misaligned as little as 5 feet (2 seconds of arc vernier acuity).
4. Two points sharply contrasted with the surrounding background separated by as little as 38 feet (15 seconds of arc minimum separable).

Why, then, was there difficulty in appreciating the visual potential of man in space? I believe that there are three reasons for the total misapprehension and that only one of them is valid.

1. The fact that much of the earth is covered by clouds is a valid restriction of visual capability. But this is not true for any specific point on the earth at all times. Therefore, if a mission is long enough, an unencumbered view of any specific area can be expected eventually.
2. It was anticipated by many people that the attenuation of the earth's atmosphere would cut down contrast to the point that vision would be useless from space. Many of these thinkers failed to

appreciate the difference between looking tangentially through the atmosphere and looking vertically through it. In the vertical view from space the attenuating layer is only about 2 miles thick, whereas on the ground or at low altitudes the entire range of view is through the most dense attenuation.

3. The most serious obstacle to appreciation has, in my opinion, been the interpretation of some key psychophysical studies. These studies were very carefully worked out to find the threshold of man's abilities to recognize targets. There is no question of the scientific excellence of the investigators or of their data or even of the importance of their work. The problem was in the extrapolation of their work to predict seeing from space. The interpreters failed to recognize the fact that when the laboratory targets were scrupulously isolated from any clues to their identity, the measurements were valid in a laboratory sense but the interpretation in terms of actual human seeing could not be simple and direct. In order to get "significant" laboratory results, the variables of intelligence and experience had to be eliminated from the tests. These two variables are the very qualities of man which make the man useful in space; their elimination must invalidate the experimental results from a practical standpoint.

### The Future of Vision in Space

If we examine the problem of vision from space in light of proven visual capabilities and available clues and then add a specifically trained, highly intelligent man, we can get some idea of the potentialities. An ordinary man only very rarely utilizes his maximal visual capability. He would therefore not be likely to see as much as an astronaut who because of his prior flying experience and his training has become accustomed to the utilization of his maximum visual capability. Thus, in spite of the belief that extra-vehicular vision would contribute little, the astronauts proved that the application of intelligent interpretation to the available clues can "resolve" fantastically small visual targets.

It is our belief that the limits of visual capability have not been reached. Specific concentration of training and achievement of visual skill in reconnaissance can be accomplished. This will enable future space crews who have more time available and a different mission orientation to see much more than has been reported to date. These men will function at the extreme limits of their capabilities utilizing color, shading, texture, lines, breaks in lines, two-point discrimination, lights and contrasts. They will, with intelligence, be able to interpret significance of lack of detail as well as the detail itself. Their preselected level of intelligence, experience, and functional integrity will provide them with much more than an ability to aim and trigger a camera or other reconnaissance device at a programmed area. These men will be able to identify unsuspected visual "targets of opportunity." Thus, through the unaided visual capability of the man in space, the usefulness of any other device will be extended in range, effectiveness, reliability and versatility.

# GLOSSARY OF TERMS FREQUENTLY USED IN OPHTHALMOLOGY

- **accommodation** the ability of the eye to adjust for various distances
- **acetylcholine** a chemical compound which is essential for the transmission of nerve impulses
- **acrylic** plastic
- **acuity, visual** expression of acuteness of vision
- **albinism, ocular** complete absence of pigment in the eyes
- **amaurosis** blindness occurring without apparent lesion of the eye
- **amblyopia** impairment of vision with no detectable organic lesion
- **ametrope** imperfection in vision; imperfection in the refractive powers of the eye
- **anabolic** constructive, as opposed to destructive, metabolism
- **aneurysm** A sac formed by the dilatation of the walls of an artery or vein and filled with blood
- **angiitis** inflammation of a vessel
- **angioma** a tumor whose cells tend to form from blood or lymph vessels
- **angle of anterior chamber** junction between iris and cornea through which the aqueous flows
- **angoid streaks** bands appearing in the retina often associated with systemic disease
- **aniridia** absence of the iris
- **anisekonia** a condition in which the image of an object as seen by one eye differs in size and shape from that seen by the other eye
- **anophthalmic** absence of the eye
- **antibody** part of defense mechanism
- **antigen** substance which induces formation of antibodies
- **aphakia** having no lens in the eye, e.g., after cataract removal
- **applanation** undue flatness, as of the cornea
- **aqueous humor** fluid in the anterior chamber of the eye
- **arcus senilis** a white ring around the margin of the cornea especially in the aged
- **asthenopia** weakness or tiring of the eyes, dimness of vision
- **astigmatism** defect in the curvature of the cornea
- **atropine** paralyzes parasympathetic nerve action; applied locally to the eye to dilate the pupil and paralyze ciliary muscle for accommodation
- **autograft** transplant one tissue of an individual back to the same individual
- **autoimmune** allergy to one's own tissue
- **axon** nerve fiber
- **bacteriophage** a bacterial virus
- **biomicroscopy** microscopic examination of the cornea or lens with a slit lamp and corneal microscope
- **blepharitis** inflammation of the eyelids
- **blepharospasm** spasm of eyelid muscles
- **blind spot** normal defect in visual field due to position at which optic nerve enters the eye
- **bulbar** referring to the eyeball
- **buphthalmos** enlargement of the eye
- **canaliculus (lacrimal)** narrow tubular passage—tear duct
- **canthus** the angle at either end of the slit between the eyelids
- **carbonic anhydrase inhibitor** a chemical compound, e.g., Diamox, which suppresses the formation of the enzyme carbonic anhydrase and in the eye decreases the formation of aqueous humor
- **caruncle** a small fleshy eminence
- **catabolic** destructive metabolism
- **cataract** an opacity of the lens
  - **incipient** any cataract in its early stages, or one which has sectors of opacity with clear spaces intervening
  - **mature** one in which the lens is completely opaque and ready for operation
  - **hypermature** the lens has become either solid and shrunken or soft and liquid
  - **congenital** one which originates before birth
  - **senile** a hard opacity of the lens occurring in the aged
  - **traumatic** cataract following an injury
- **choked disc** swelling of the optic nerve
- **chorioretinitis** inflammation of the choroid and retina
- **choroid** vascular layer of the eyes—its function is to nourish the retina
- **ciliary body** portion of vascular layer of eye whose function is secretion of aqueous humor
- **coloboma** a congenital defect in which a portion of a structure of the eye is absent
- **cone, retinal** specialized visual cells in the retina, responsible for sharpness of vision and color vision
- **conical cornea, keratoconus** a conical protrusion of the cornea
- **conjunctiva** the delicate membrane that lines the eyelids and covers the exposed surface of the eyeball
- **contact lens, corneal** contact lens molded for the cornea only
- **contact lens, scleral** contact lens molded to the entire globe, not containing the cornea
- **corticosteroids** cortisone derivatives
- **cryosurgery** use of low temperature in surgery
- **cup, optic** depression in the center of the optic disc (nerve)
- **cyclitis** inflammation of the ciliary body
- **cycloplegia** paralysis of the ciliary muscle
- **cytomegalic inclusion disease** retinal viral inflammation
- **dacryocystitis** inflammation of the lacrimal sac
- **demyelinizing** loss of protective myelin sheath of nervous tissue, e.g. in multiple sclerosis
- **densitometry** measurements of blood flow by determination of density of dyes introduced into the circulation
- **detachment of retina** a condition in which the inner layers of the retina are separated from the pigment layer
- **diathermy** coagulation of tissue by heat such as used in retinal detachment surgery
- **diopter** a unit to designate the refractive power of a lens
- **diplopia** double vision
- **disc, optic** the optic nerve as it enters the eye
- **electroretinogram** a record of the changes of potential in the retina after stimulation by light
- **emmetropia** perfect vision
- **endophthalmitis** inflammation of the internal structures of the eye
- **enucleation** surgical removal of the eye
- **enzyme** an organic compound, frequently a protein, capable of accelerating or producing some change in another chemical compound for which it is often specific
- **esophoria** a tendency to deviation of a visual axis toward the other eye
- **esotropia** actual deviation of the visual axis toward that of the other eye ("crossed eyes")
- **etiology** the cause of a disease
- **exenteration** surgical removal of the contents of a body cavity, e.g. the orbit
- **exophoria** a tendency to deviation of a visual axis away from that of the other eye when fusion is prevented
- **exophthalmos** abnormal protrusion of the eyeball
- **exotropia** deviation of a visual axis away from that of the other eye, "wall eye"
- **extraction** the surgical removal of the lens, e.g., cataract removal
- **flash blindness** visual disturbance resulting from intense light source, e.g., atomic bomb blast
- **fluorescein** a fluorescent yellowish dye which is used in determining the fit of contact lenses or in the detection of corneal abrasions; also may be injected intravenously to study blood vessel pathology of the eye
- **fovea** a depression or pit in the center of the macula; it is the area of clearest vision
- **fundus** the interior of a hollow organ as the eye
- **geniculate body** a way station in the central nervous system for the transmission of visual impulses from the retina to the visual cortex of the brain
- **glaucoma** a condition of the eye characterized by increased intraocular pressure
  - **acute, closed angle** glaucoma caused by obstruction of the filtration angle by the base of the iris
  - **chronic simple, open angle** glaucoma in which the angle of the anterior chamber is open and free from obstruction
  - **congenital** glaucoma present at birth due to a defect in the angle of the anterior chamber
  - **absolute** a final, hopeless stage in which vision is completely and permanently lost
- **glioma** a tumor derived from nerve tissue
- **gonioscopy** examination of the anterior chamber of the eye
- **gonorrheal ophthalmia** blinding eye disease of newborn infants acquired in the birth canal

**hemianopia** defective vision or blindness in half of the visual field

**herpes simplex** an acute virus disease marked by groups of watery blisters on the skin and mucous membranes; the most common cause of blindness due to corneal disease

**herpes zoster** an acute inflammatory disease affecting nerve tissue; shingles

**heterograft** transplant from one species, e.g., monkey, to another species, e.g., man

**histoplasmosis** parasitic inflammation affecting eye

**homograft** transplant from one member of a species, e.g., man to another member of the same species

**hypermetrope** farsightedness

**hyphaema** hemorrhage into the anterior chamber of the eye

**hypophysectomy** removal of pituitary gland

**IDU** antimetabolic chemical agent, iododesoxyuridine, used as antiviral agent in ophthalmology

**implant** an inert filler placed in the eye socket after surgical enucleation

**infra-red heat scanning** temperature sensitive techniques for diagnosis

**intracapsular** *(adj.),* removal of the lens with the lens capsule intact

**intraocular pressure** the pressure of the fluid within the eye

**iridectomy** surgical removal of part of the iris

**iridocyclitis** inflammation of the iris and the ciliary body

**iritis** inflammation of the iris

**ischemic** lacking in blood

**keratitis** inflammation of the cornea; usually characterized by loss of transparency and dullness

**keratoconus** conical cornea, a conical protrusion of the cornea

**keratoprosthesis** corneal implant usually of plastic material, artificial cornea

**lacrimal** pertaining to the tears, or to the structure conducting or secreting tears

**lagophthalmos** a condition in which the eye cannot be completely closed

**lamellar** with reference to corneal transplant means removing partial thickness of cornea

**lens** lens of the eye: a transparent biconvex body situated between the posterior chamber and the vitreous through which the light rays are focused on the retina

**lenticular** *(adj.),* pertaining to or shaped like a lens

**leukoma** a dense white opacity of the cornea

**levator muscle** muscle which raises the eyelid

**limbus** a border; the edge of the cornea where it joins the sclera

**macula** an oval area in the center of the retina devoid of blood vessels; most responsible for color vision

**melanoma** a tumor arising from pigmented tissue (nevus)

**microphthalmos** a rare developmental defect in which the eyeballs are abnormally small

**millimeter** one-tenth (1/10) of a centimeter; 2.54 centimeters = 1 inch

**miosis** reduction in the size of the pupil

**miotic** a drug which causes a reduction in the size of the pupil

**muscae volitantes** normal small floating spots seen when looking at a bright uniform field as the sky; attributed to minute remnants of embryonic structure in the vitreous humor

**mydriasis** increase in pupil size

**myopia** nearsightedness

**myopic degeneration** a form of nearsightedness which may lead to blindness

**needling (of cataract)** a surgical procedure in which the lens is punctured to allow the absorption of the lens substance

**neuritis, optic** inflammation of a nerve, e.g., the optic nerve

**retrobulbar** inflammation of the orbital portion of the optic nerve

**neuroblastoma** retinoblastoma

**nucleus** a central mass, portion, or core

**nystagmus** a regular, rapid characteristically involuntary movement or rotation of the eye

**oculist** an old term for ophthalmologist, still used in England

**oculomotor** *(adj.)* pertaining to the movements of the eye

**onchocerciasis** parasitic infection common in tropical areas

**opacity** the condition of being opaque

**ophthalmodynamometer** an instrument for measuring the blood pressure in the retinal artery

**ophthalmologist** a medical practitioner specializing in the medical and surgical care of the eyes

**ophthalmoscopy, direct** the observation of an upright mirrored image of the interior of the eye

**ophthalmoscopy, indirect** the observation of an inverted image of the interior of the eye

**optic atrophy** degeneration of the optic nerve fibers; visual loss usually accompanies this condition

**optic chiasm** an arrangement of nerve fibers in which the optic nerves of both eyes cross at a junction near the pituitary gland

**optic disc** the portion of the optic nerve within the eye which is formed by the meeting of all the retinal nerve fibers at the level of the retina

**optic neuritis** inflammation of the optic nerve

**optician** one who designs or manufactures optical instruments, glasses

**optometrist** an expert in optometry; nonmedical visual care

**ora serrata** one of the sites of attachment of the retina to the choroid

**orbicularis** an eyelid muscle which closes the eye

**orbit** the cavity in the skull which contains the eyeball

**orthoptics** the teaching and training process for the elimination of strabismus

**paddy keratitis** corneal inflammation in rice field workers, cause unknown

**pallor of disc** paleness of the optic nerve, suggesting atrophy

**palpebral** *(adj.)* pertaining to an eyelid

**palsy** paralysis

**panophthalmitis** inflammation of all the structures of the eye

**papilledema** non-inflammatory edema of the optic nerve head

**paracentesis** surgical puncture of a cavity for the aspiration of fluid, e.g., aspiration of aqueous humor

**parasympathetic** *(adj.)* the nerve system which, in the eye, activates pupillary constriction

**parasympathomimetic** a chemical agent that produces effects similar to those produced by stimulation of the parasympathetic nerves

**paresis** incomplete or partial paralysis

**pathogenesis** sequence of abnormal events causing a disease

**pathway, visual** the neural path of visual impulses

**pemphigus** a progressive and often fatal condition of blistering and scarring of the mucous membranes and the skin which can affect the eye

**penetrating** with reference to corneal transplant means removing full thickness corneal segment from epithelium to endothelium

**perimeter** an instrument for measuring the field of vision

**periphlebitis** inflammation of the tissues around a vein

**phakoma** a small grayish white tumor in the retina

**phenothiazine** a chemical compound forming the base of many currently used tranquilizers

**phlyctenule** a minute ulcerated nodule of the cornea or conjunctiva

**phoria** any tendency to deviation of the eyes from normal

**photophobia** abnormal sensitivity to and discomfort from light

**phthisis bulbi** shrinking, wasting, and atrophy of the eyeball

**pigment epithelium** a layer of cells in the retina containing pigment granules

**pilocarpine** a substance that causes the pupil to contract

**pituitary ablation** destruction of pituitary gland

**pleoptics** a technique of eye exercises designed to develop fuller vision and binocular cooperation

**posterior pole of eye** the center of the posterior curvature of the eyeball

**presbyopia** impairment of vision due to advancing years or old age

**prosthesis** artificial, e.g., eye

**pterygium** a growth of the conjunctiva considered to be due to a degenerative process caused by long continued irritation as from exposure to wind and dust

**ptosis** a paralytic dropping of the upper eyelid

**pupil** the opening at the center of the iris of the eye for the transmission of light

**pyrogenic** producing temperature elevation

**radiation, optic** a structure in the brain made up of nerve fibers from the retina

**rectus muscle** a muscle attached to the eyeball which controls eye movements

**reflex, corneal** blinking or winking in response to tactile stimulation of the cornea; reflection of light from the cornea

**reflex, oculo-cardiac** a slowing of the rhythm of the heart following compression of the eyes; if ocular compression produces acceleration of the heart, the reflex is called inverted

**reflex, pupillary** constriction of the pupil when stimulated by light

**refraction** the determination of the refractive errors of the eye and their correction by glasses

**refractive errors** a defect in the eye that prevents light waves from being brought to a single focus exactly on the retina

**retina** the innermost of the three tunics of the eyeball, surrounding the vitreous body and continuous posteriorly with the optic nerve

**retinal correspondence** corresponding retinal areas in both eyes which perceive the same point in space simultaneously

**retinal hole** a space where the retina has pulled away from the underlying choroid tissue

**retinitis pigmentosa** an hereditary degeneration and atrophy of the retina

**retinoblastoma** a tumor arising from retinal germ cells; glioma of the retina

**retino-choroiditis** inflammation of the retina and the choroid

**retinopathy** a disease of the retina due to various causes

- **diabetic** changes in the retina due to diabetes mellitus
- **hypertensive** a disease of the retina associated with essential or malignant hypertension

**retinoscope** an instrument for measuring the refractive state of the eye

**retrobulbar** situated or occurring behind the eyeball

**retrolental fibroplasia** a disease of the retina in which a mass of scar tissue forms in back of the lens; associated with premature birth and oxygen inhalation

**rubeosis iridis** condition characterized by a new formation of vessels and connective tissue on the surface of the iris

**sac, conjunctival** the potential space, lined by conjunctiva, between the eyelids and the eyeball

**sac, lacrimal** the dilated upper end of the nasolacrimal canal

**sarcoidosis** disease of unknown cause affecting almost all systems of the body and frequently the eye

**Schlemm's canal** a circular channel at the junction of the sclera and cornea through which aqueous humor leaves the eye

**sclera** the tough, white, protective coat of the eye

**scotoma** a blind or partially blind area in the visual field

**screen, tangent** a large square of black cloth, stretched on a frame, and having a central mark for fixation used to map the field of vision

**segment, anterior** referring to the front part of the eye

**separation of retina** separation of the retina from its pigment epithelium layer

**silicone** plastic available in solid or liquid form

**slit-lamp** an instrument producing a slender beam of light for illuminating any reasonably transparent structure, as the cornea

**spasm, lid (blepharospasm)** a sudden, violent, involuntary contraction of the eyelid, attended by pain

**spectrum, visible** that portion of the entire spectrum which contains wave lengths capable of stimulating the retina

**squint** strabismus

**squint, accommodative** that which is due to excessive or deficient accommodative effort

- **convergent** that in which the visual axes converge; cross eyed
- **divergent** that in which the visual axes diverge (exotropia)
- **paralytic** due to paralysis of an eye muscle

**staphyloma** protrusion of the cornea or sclera resulting from inflammation

**stereopsis** visual perception of depth or three-dimensional space

**stereotactic surgery** use of three-dimensional localization in surgery

**strabismus** squint; failure of the two eyes simultaneously to direct their gaze at the same object because of muscle imbalance

**stye (hordeolum)** inflammation of one or more of the sebaceous glands of the eyelids

**subluxation** incomplete dislocation of the lens

**sympathetic ophthalmia** inflammation of one eye due to an injury in the other eye

**syndrome** a set of symptoms which occur together; a symptom complex

**synechia** adhesions, usually of the iris to the cornea or lens

**tarsal plate** the framework of connective tissue which gives shape to the eyelid

**tarsorrhaphy** surgical attachment of upper and lower lids

**tear film** microscopic film which constantly bathes cornea

**temporal** *(adj.)* pertaining to the lateral region of the head

**Tenon's capsule** the fibrous membrane surrounding the sclera

**test object** an object, pattern, or design used for vision testing

**thromboendarterectomy** surgical removal of clot from inner lining of blood vessel

**tonography** the recording of changes in intraocular pressure produced by the constant application of a known weight on the globe of the eye

**tonometer** an instrument for measuring the pressure inside the eye

**toxoplasmosis** infection with, or a condition produced by the presence of, organisms of the genus Toxoplasmosis

**TPI** treponema pallidum immobilization test—for detection of syphilis

**trachoma** a chronic, contagious, viral infection of the conjunctiva and the cornea

**transillumination** the passage of light through body tissues for purposes of examination

**tumbling (cataract)** technique of removing cataract

**ulcer, corneal** pathological loss of substance of the surface of the cornea, due to progressive erosion and death of the tissues

**ultrasound** use of high frequency sound waves—for diagnosis and treatment

**uniocular** *(adj.)* pertaining to or affecting but one eye

**uveitis** inflammation of the vascular coat of the eye (choroid, ciliary body and the iris)

**vision, central** that which is elicited by stimuli impinging directly on the macula

**vision, distant** vision for objects at a distance (usually 20 feet or six meters)

**vision, near** vision for objects at a distance corresponding to normal reading distance (13 to 16 inches)

**vision, peripheral** that which is elicited by stimuli falling on areas of the retina distant from the macula

**vision, photopic** vision attributed to cone function characterized by the ability to discriminate colors and small detail; daylight vision

**vision, scotopic** vision attributed to rod function characterized by the lack of ability to discriminate colors and small detail and effective primarily in the detection of movement and low luminous intensities

**visual acuity** ability of the eye to perceive the shape of objects in the direct line of vision

**visual axis** the line of gaze

**visual cortex** final station of visual impulses in the brain; sensory area of brain responsible for vision

**visual field** the area of physical space visible to an eye in a given position

**vitreous or vitreous body** transparent, colorless mass of soft gelatinous material filling the eyeball behind the lens

**water drinking test** provocative test for glaucoma; the patient drinks one quart of water after fasting and the intraocular pressure is measured every 15 minutes

**xerophthalmia** conjunctivitis with atrophy and no liquid discharge; produces a dry, lusterless condition of the eyeball

**zonule of Zinn** the suspensory apparatus of the lens

**zoster** an encircling structure

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